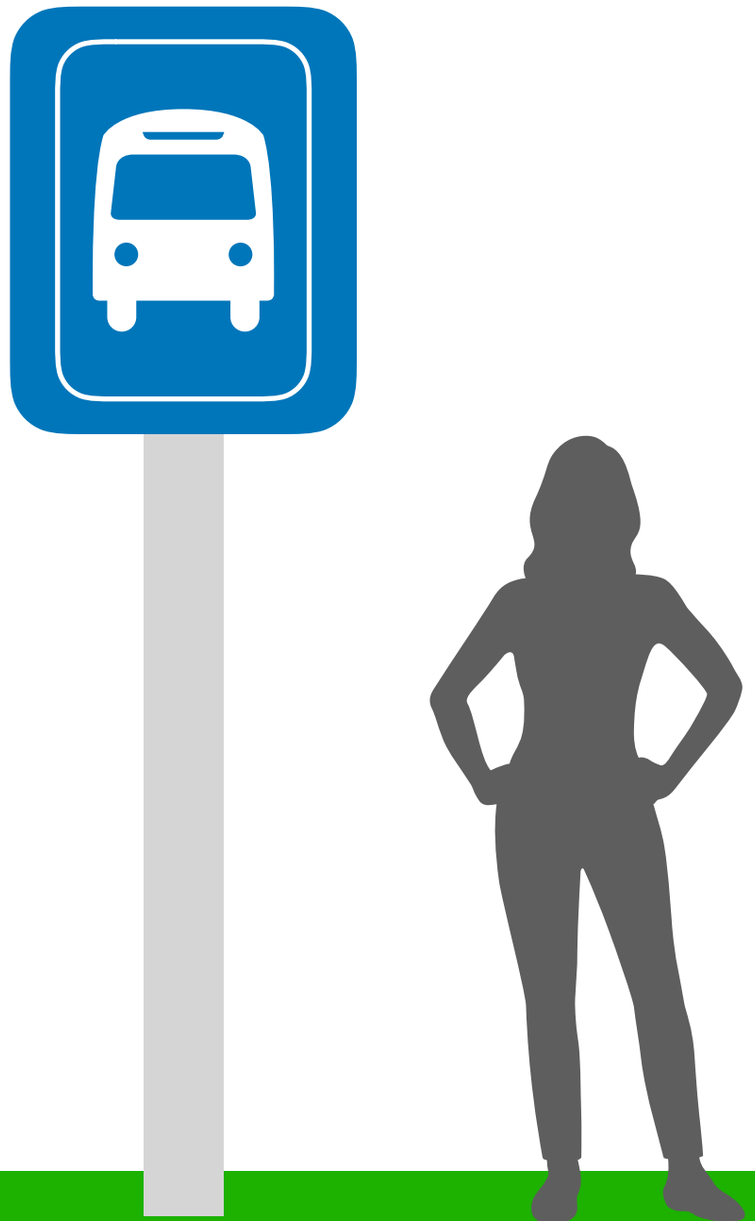
Lecture 9

Models of evolution
Botany 563 — Spring 2021

- **Previous class check-up:**
    - We studied the distance and parsimony methods and their strengths and weaknesses
- **Learning Objectives:** At the end of today's session, you will be able to
    - Explain the main characteristics of the substitution model in molecular evolution
    - Assess whether existing literature provide sufficient details on the model assumptions
- **Pre-class work**
    - Read HAL 1.1

What is a model?

Example



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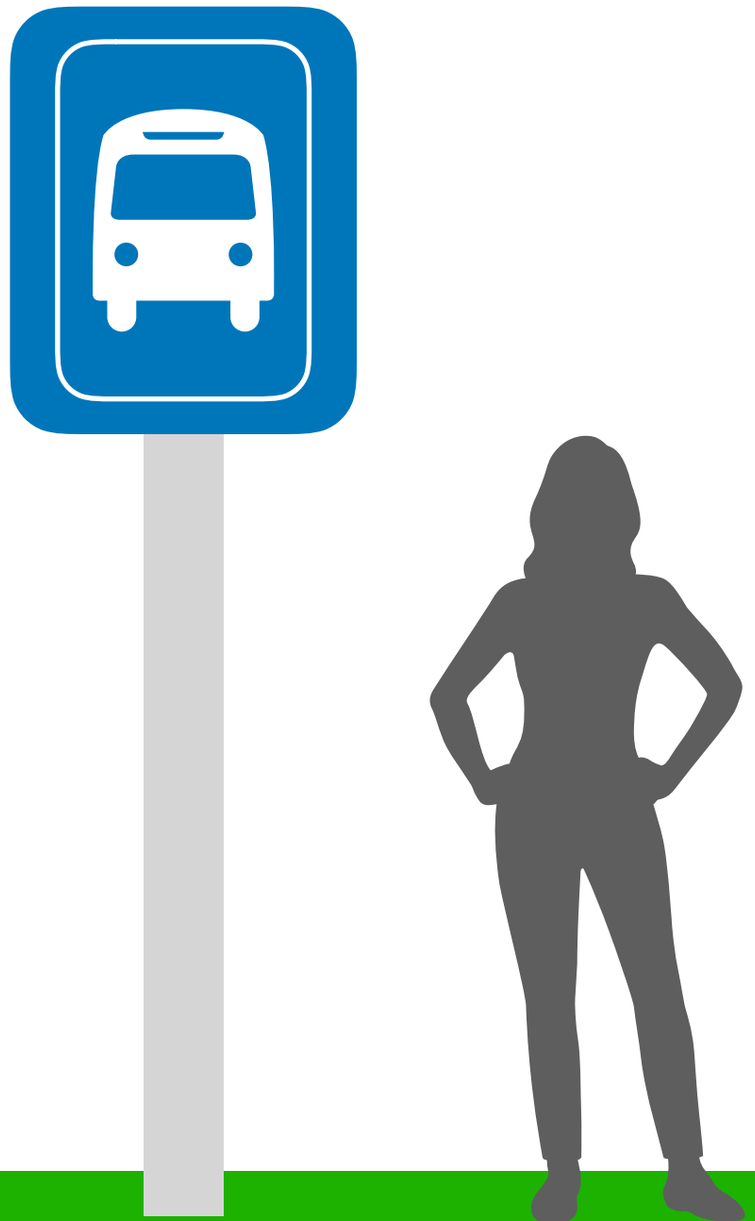

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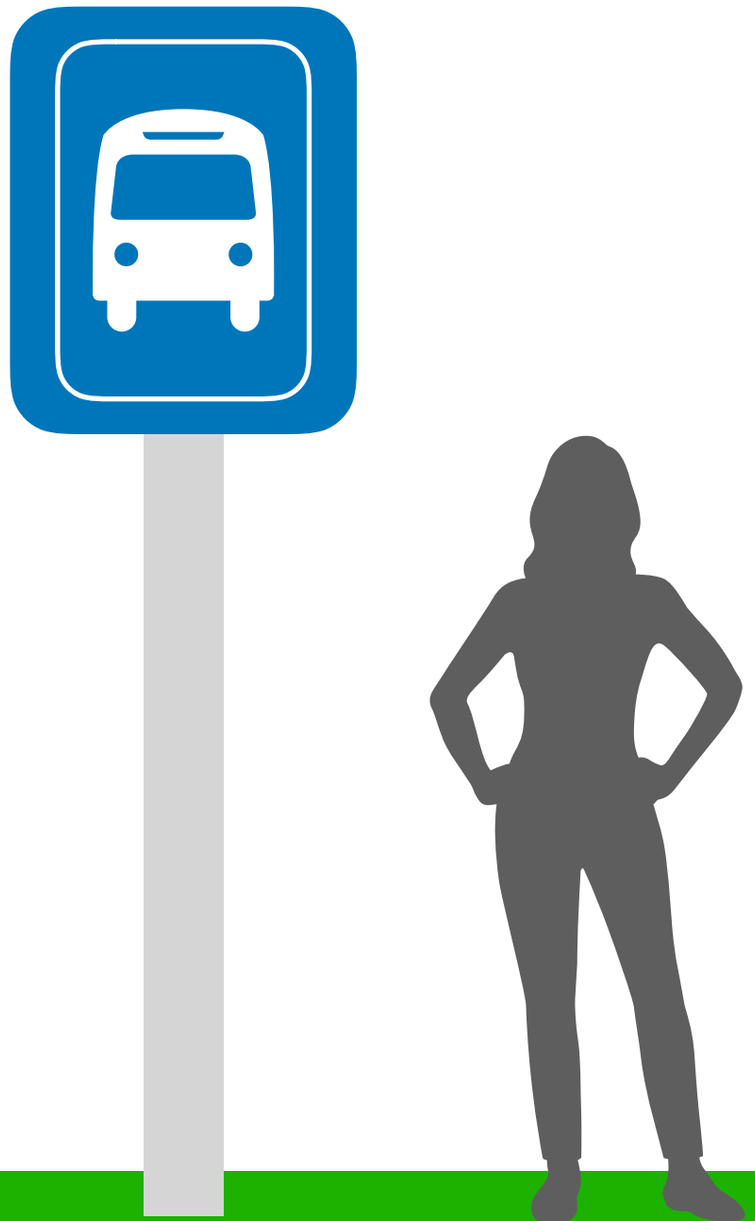

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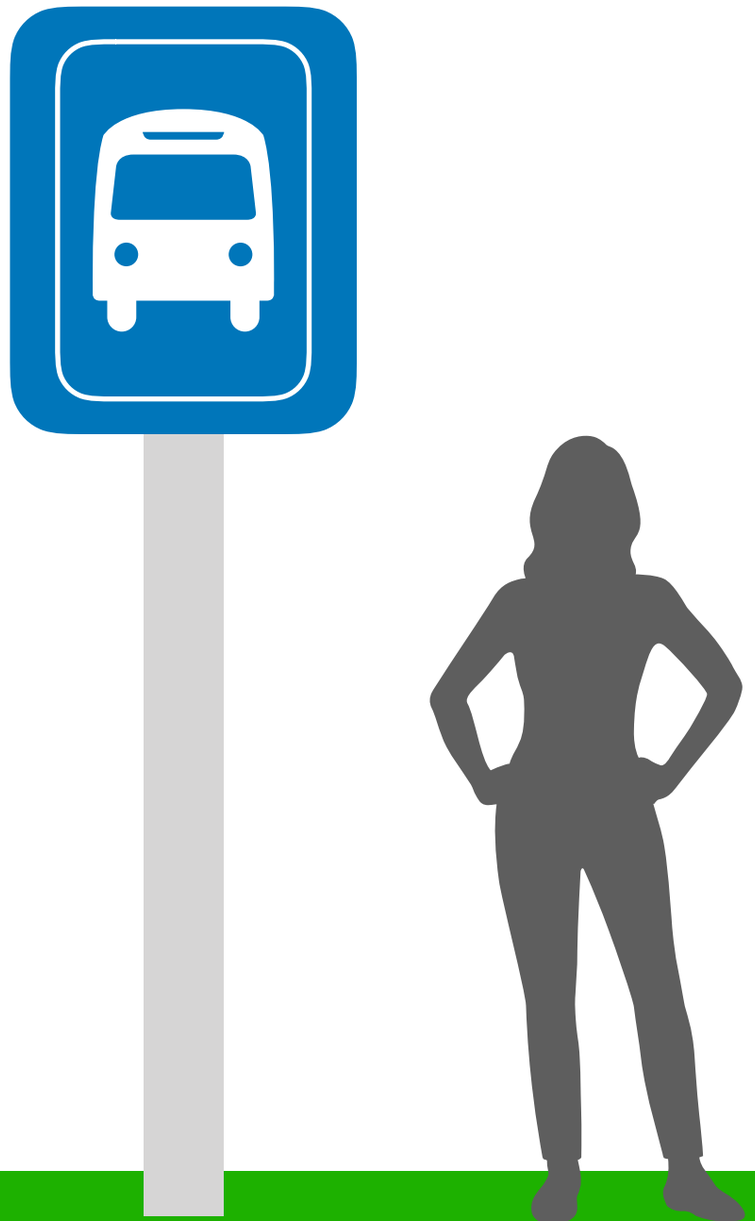

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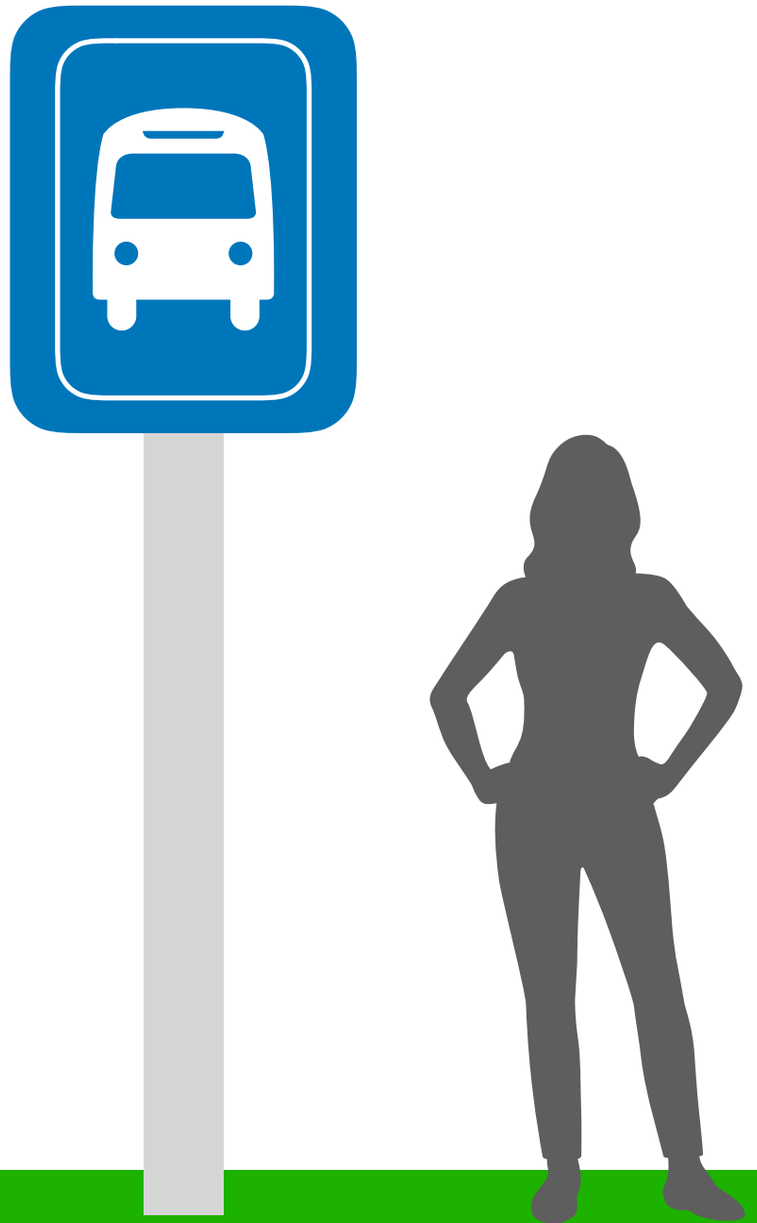
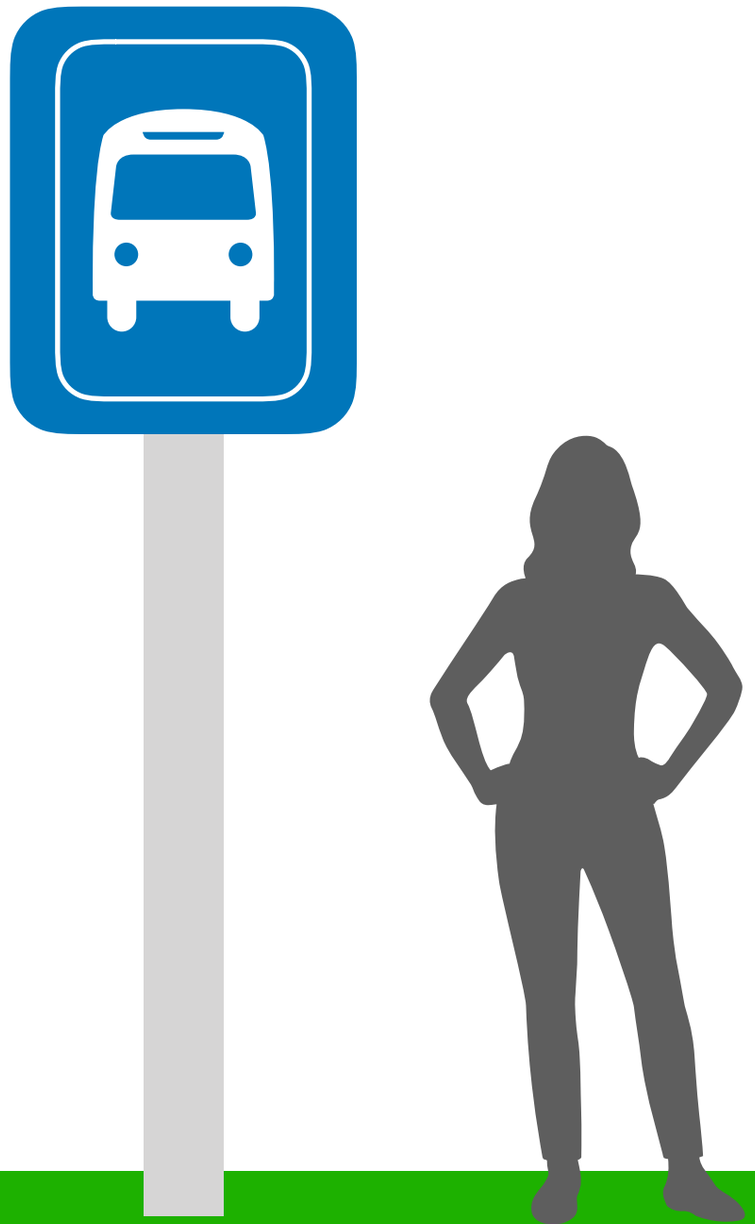


How can you predict the number of bikes that you will see the next day?

Example



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Count the number of bikes for n days and then use the average to predict

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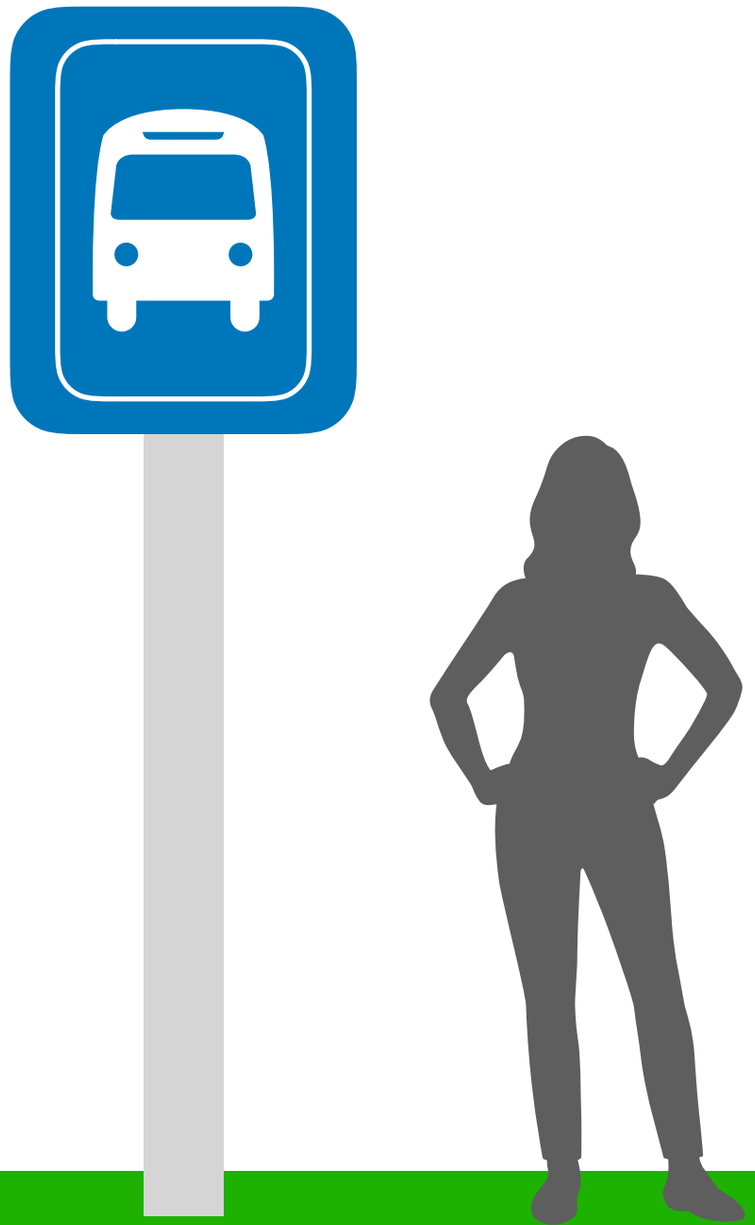
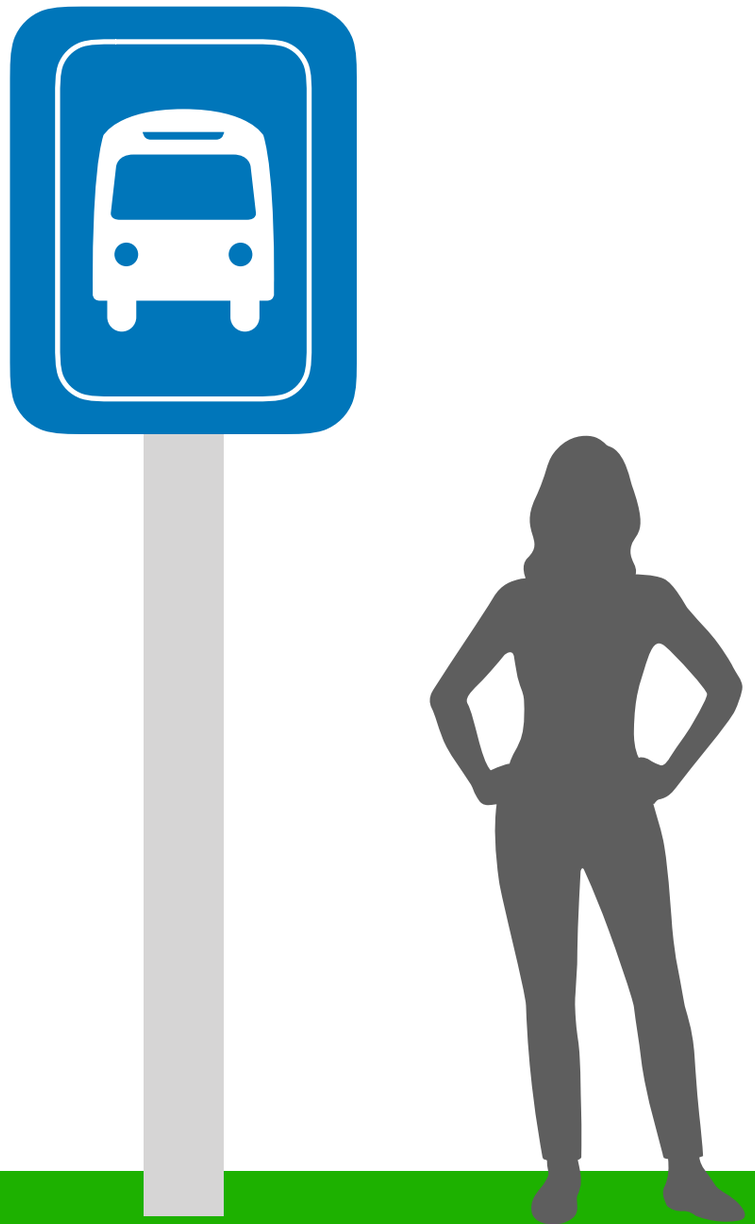


How can you predict the number of bikes that you will see the next day?

Count the number of bikes for n days and then use the average to predict

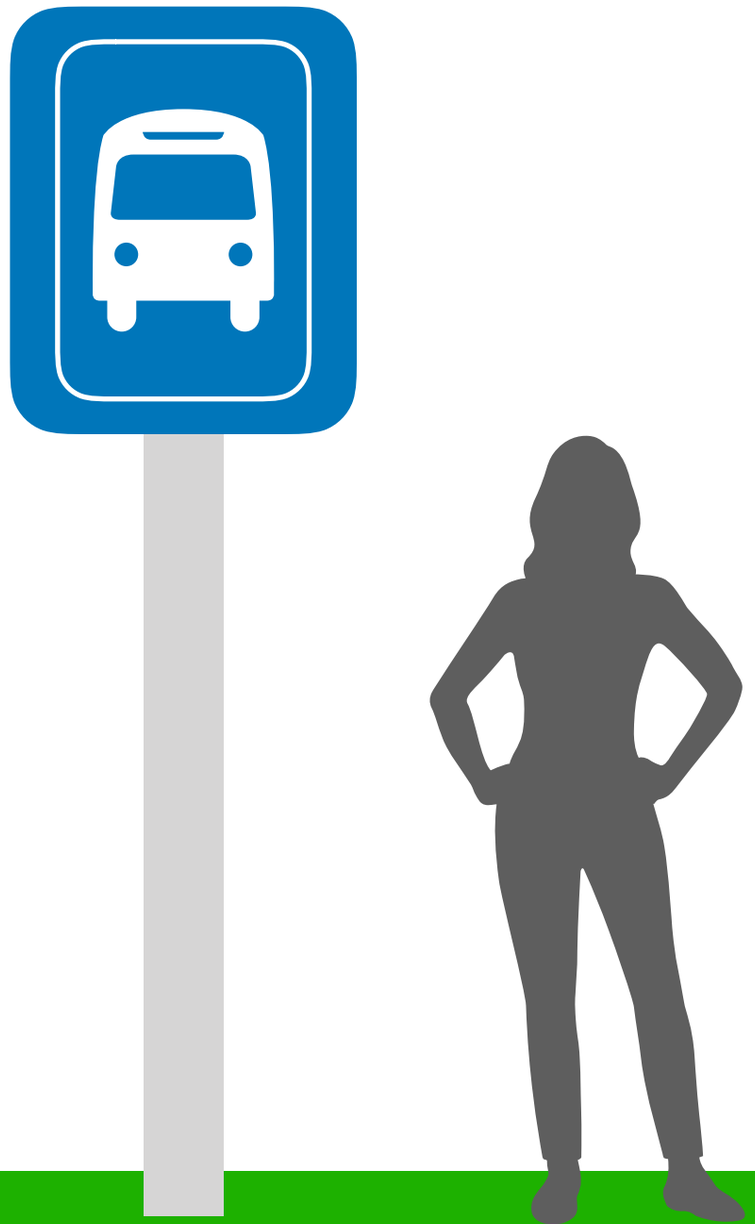
The process is random, so you don’t expect to be correct, you only get a ballpark

Example



What if you want to estimate the probability that you will see 5 bikes or 0 bikes?

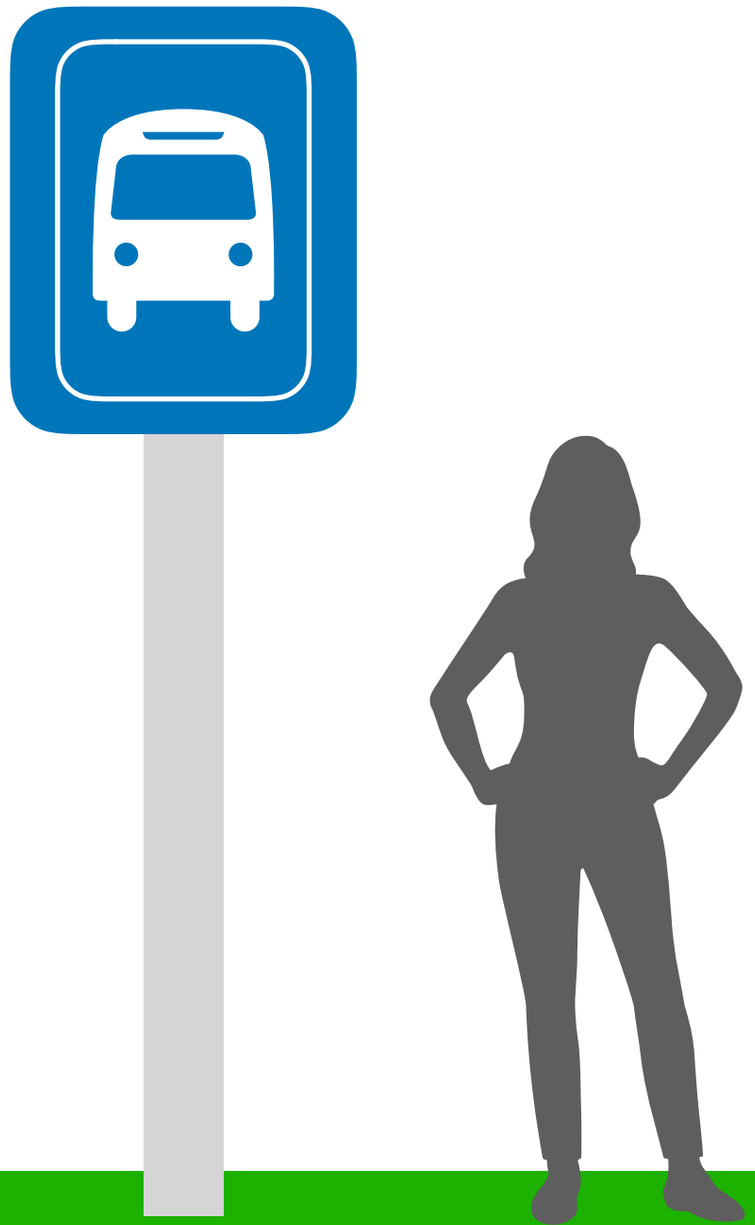
Example



What if you want to estimate the probability that you will see 5 bikes or 0 bikes?

Now you need a probability model!

Example



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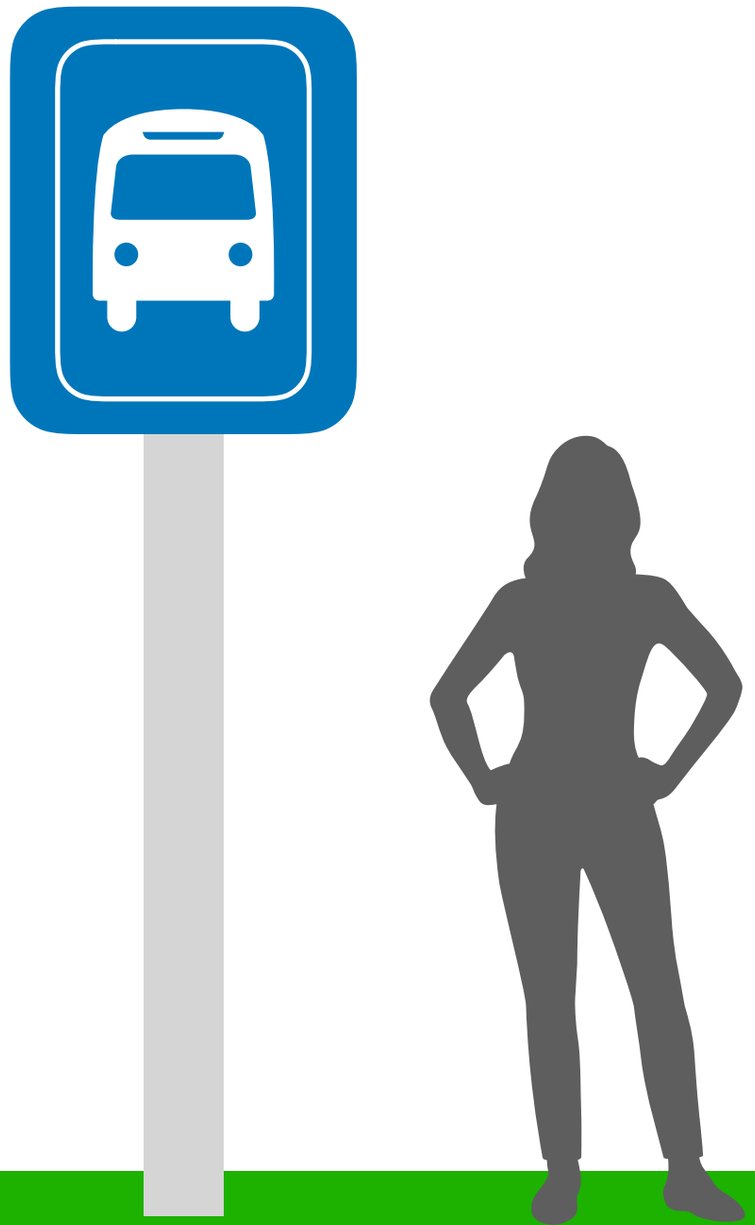
↓

P(x)

Example



What if you want to estimate the probability that you will see 5 bikes or 0 bikes?

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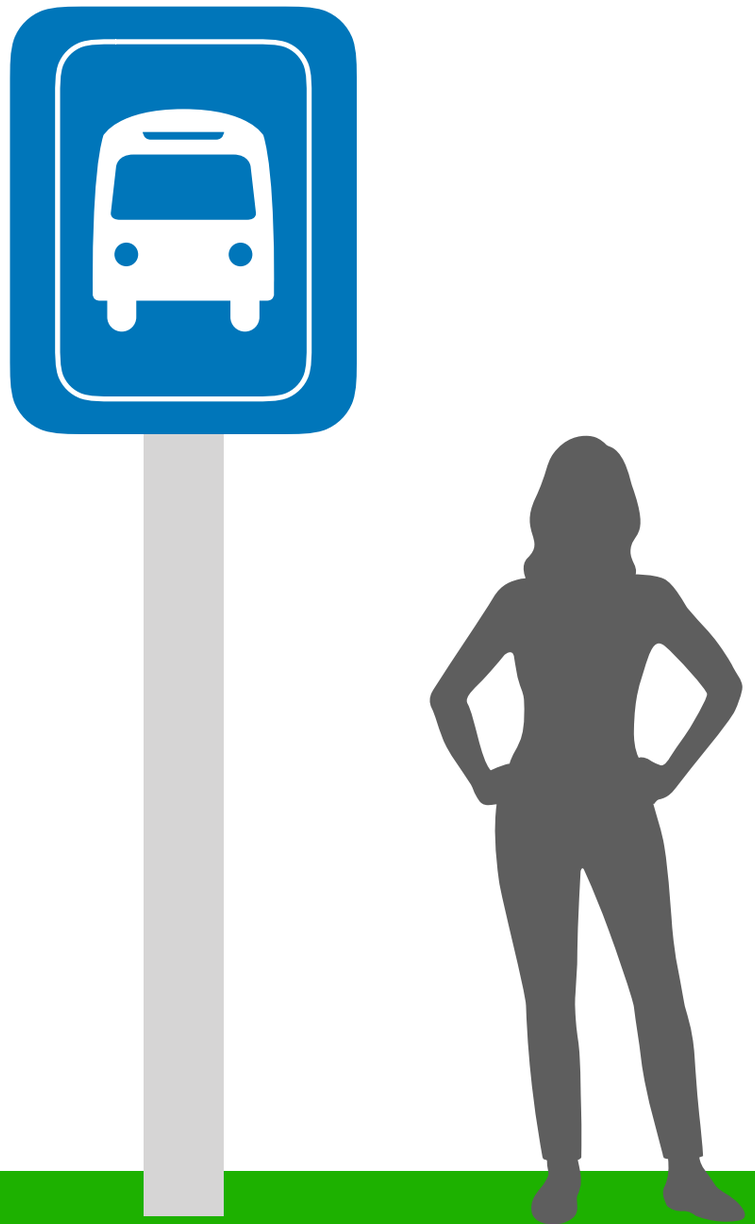
P(x)

P(5) : probability of observing 5 bikes
P(0) : probability of observing 0 bikes

Example



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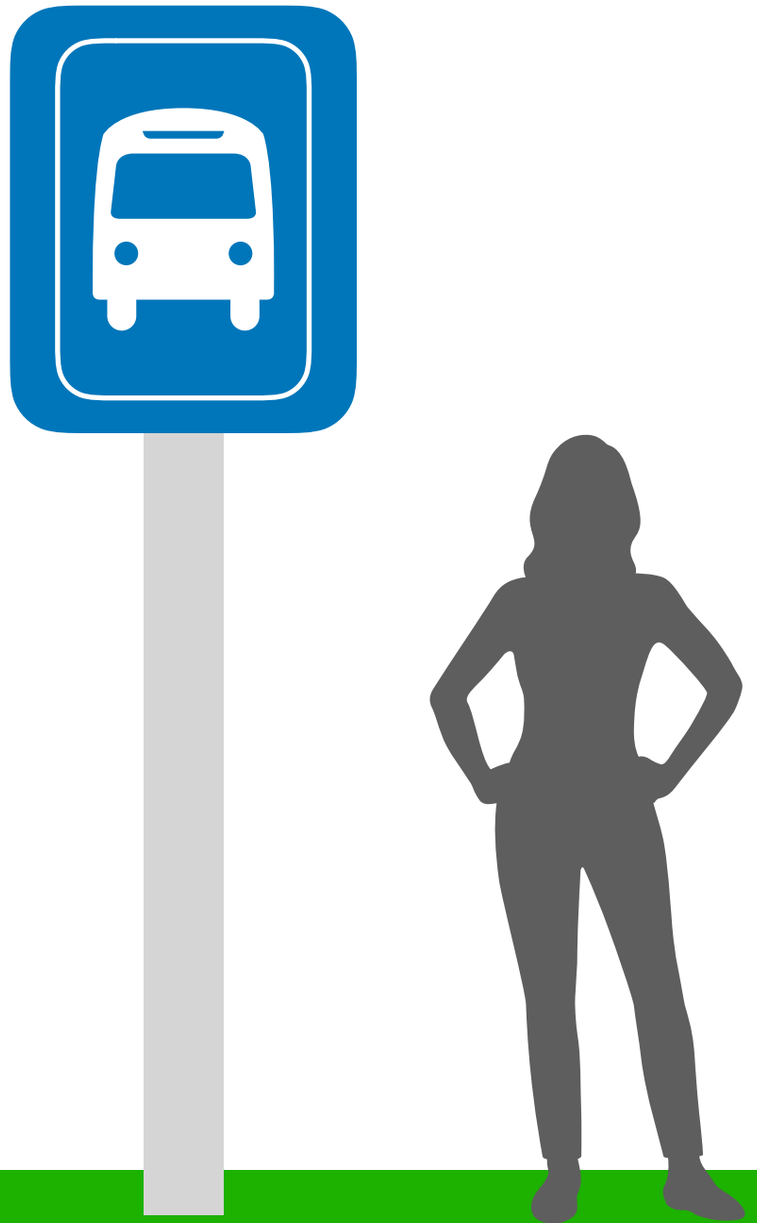
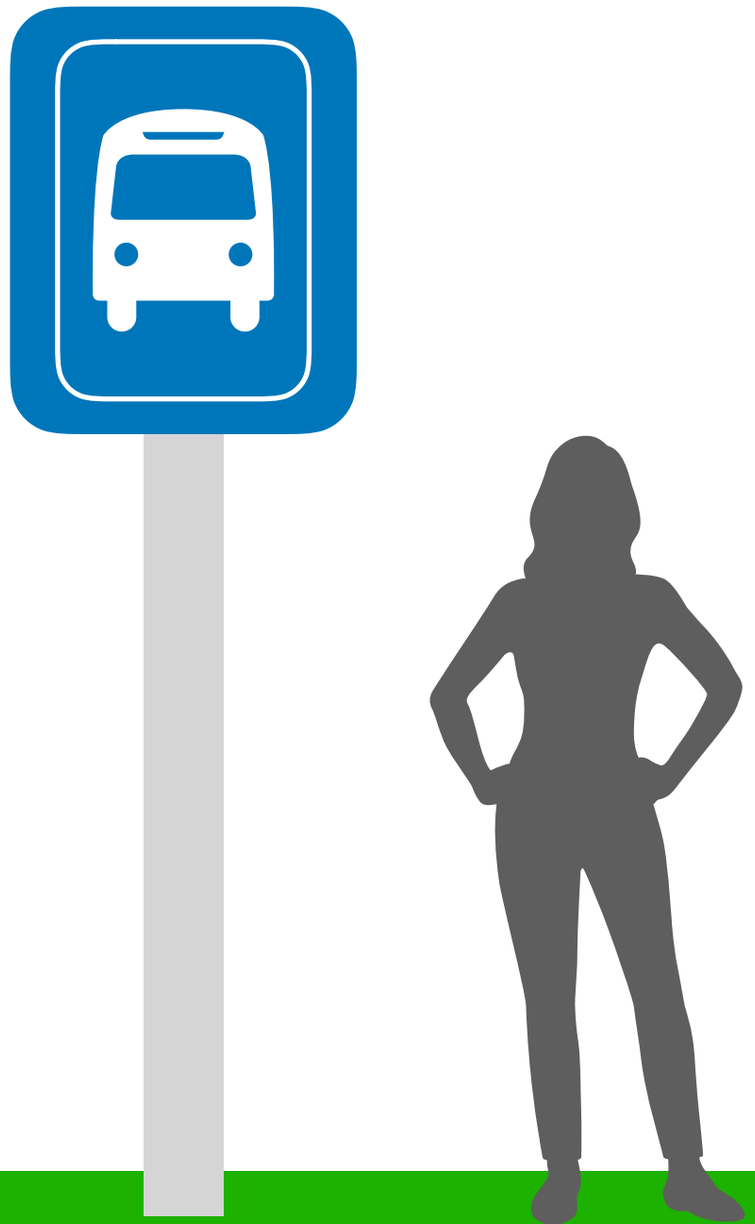


Now you need a probability model!

Assumptions:

- Symmetric around the mean?
- Not symmetric around the mean?
- How variable?

Example



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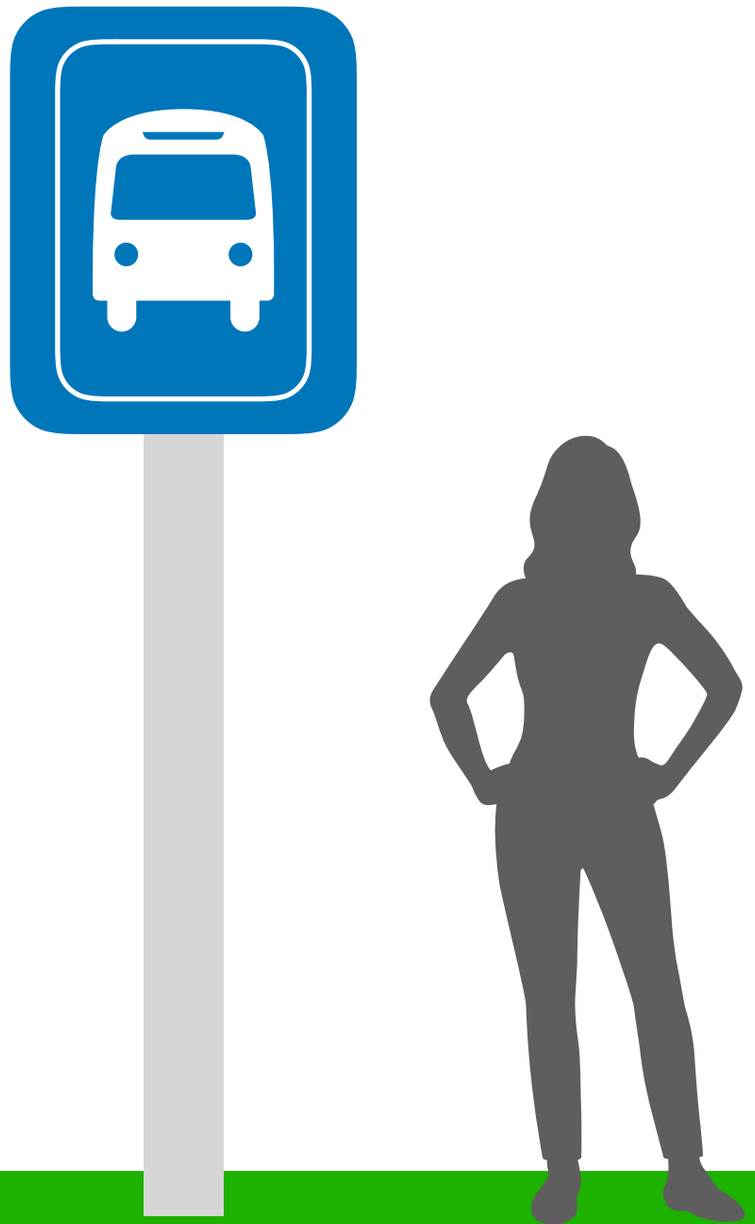

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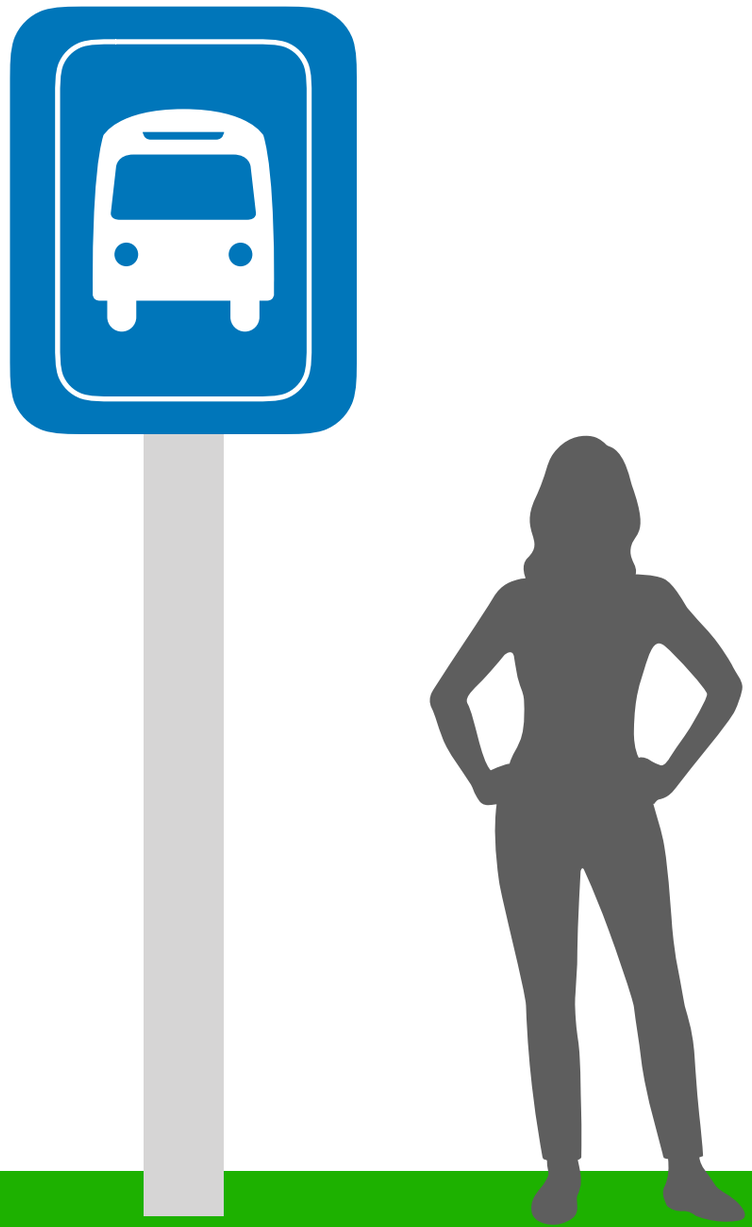
You investigate that the Poisson model
is a widely used model for counts

Example



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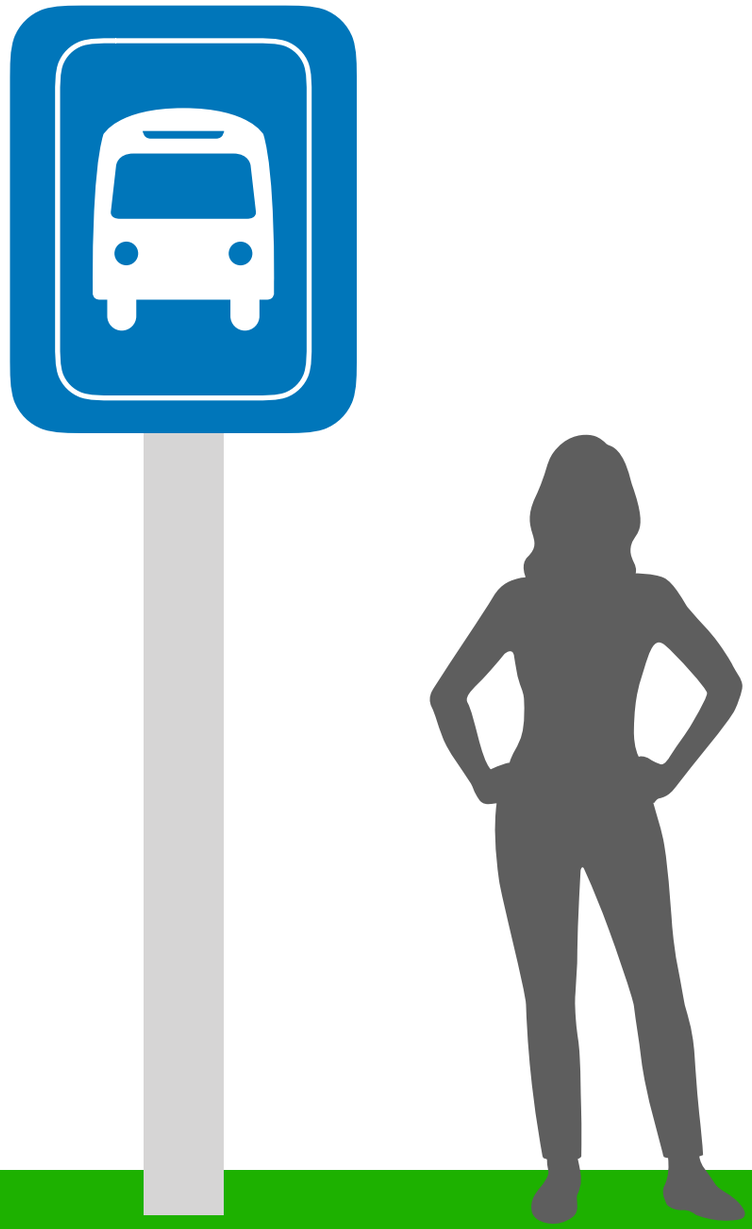
You investigate that the Poisson model is a widely used model for counts

$$P(X = k) = \frac{\lambda^k e^{-\lambda}}{k!}$$

Example



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Average

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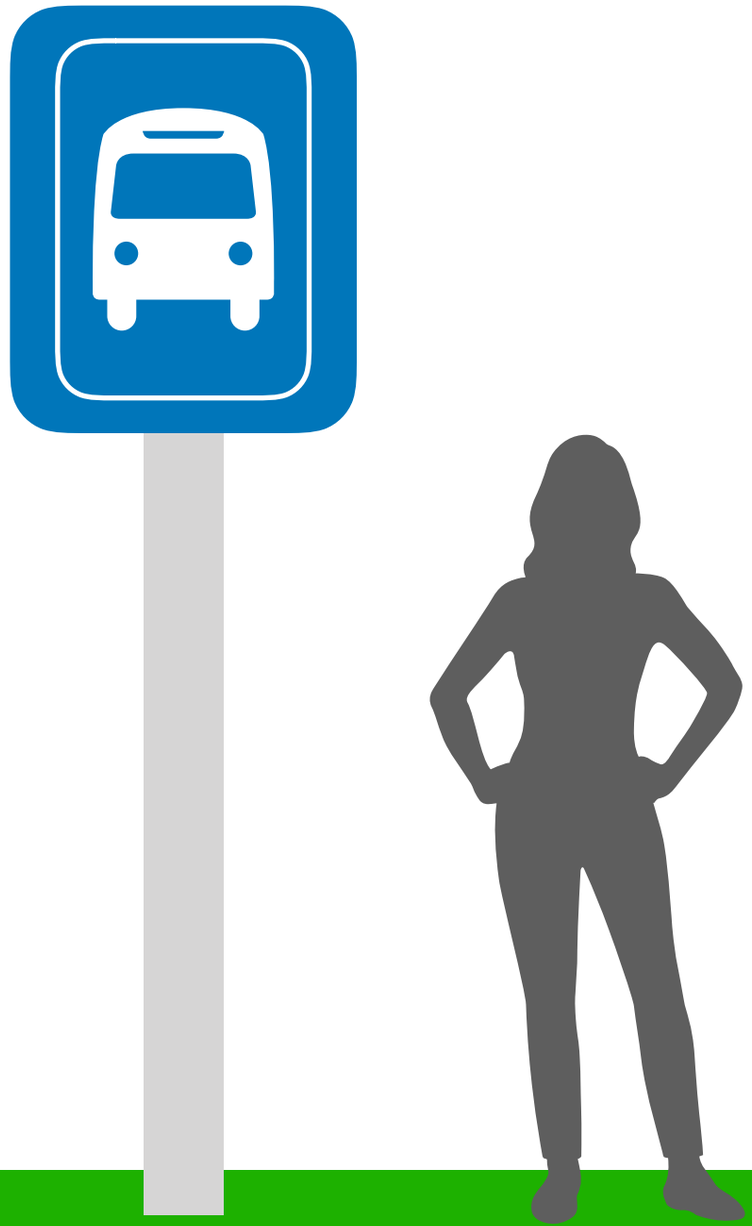

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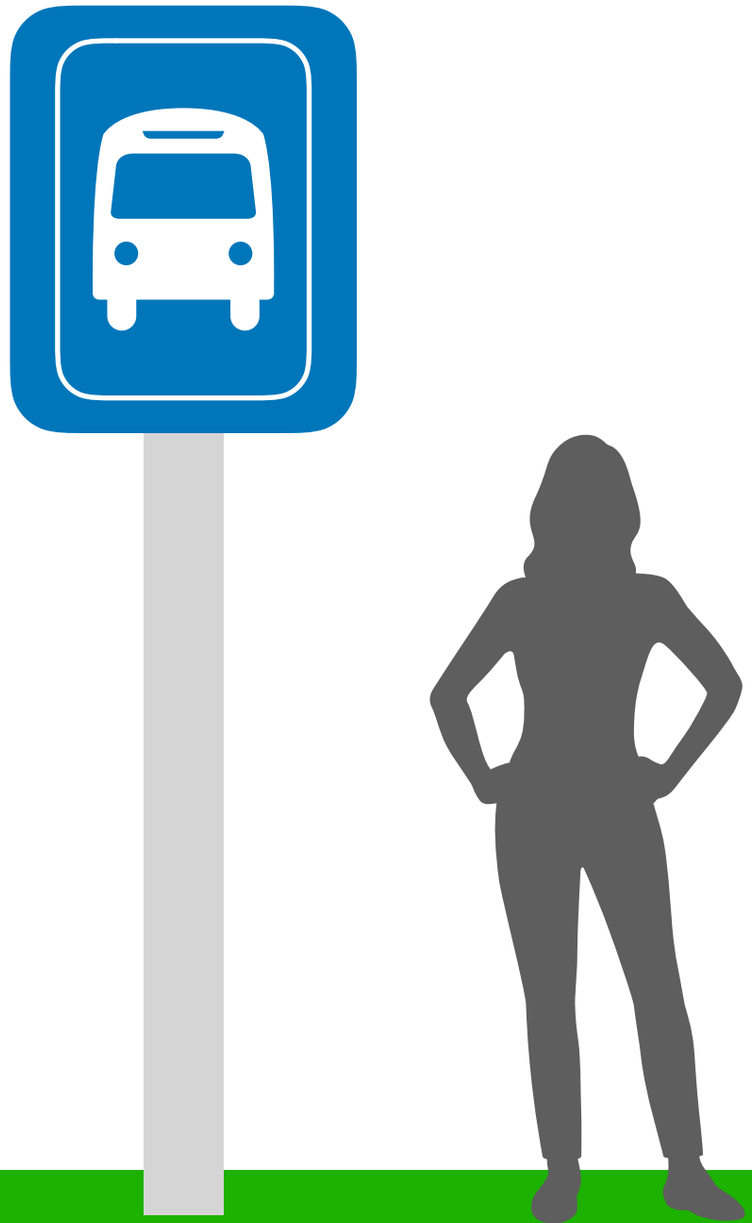
Average

Let's say that the average number of bikes you see per day is 8.4

P(X=5) = 0.07837
P(X=0) = 0.00022

https://stattrek.com/online-calculator/poisson.aspx

Example



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Average

Let’s say that the average number of bikes you see per day is 8.4

P(X>0) = 0.99978
P(X>7) = 0.60135

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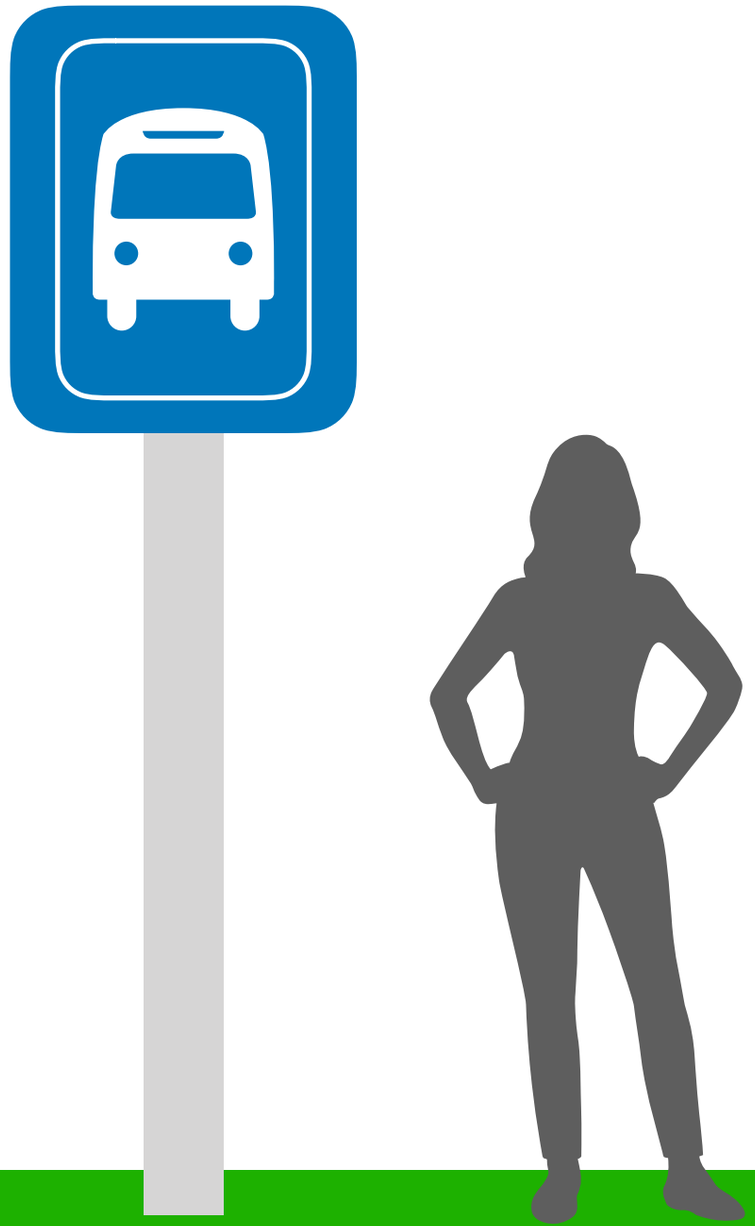
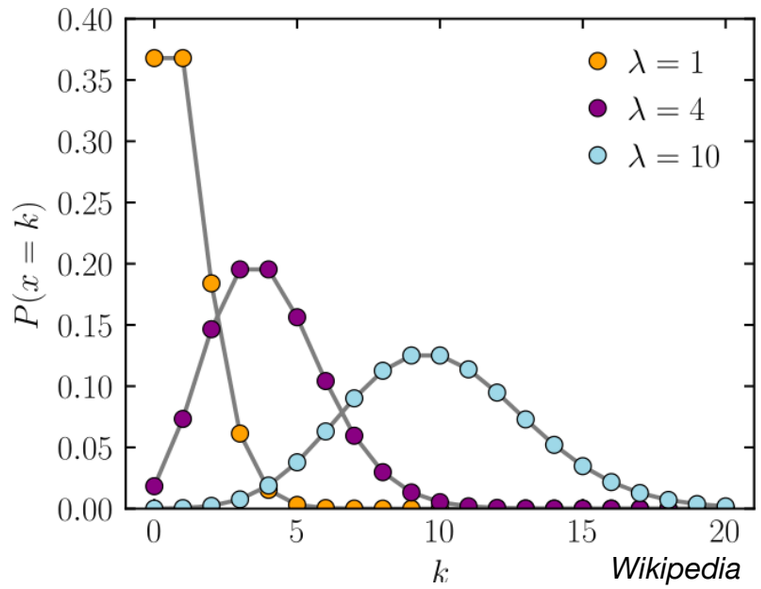
Example

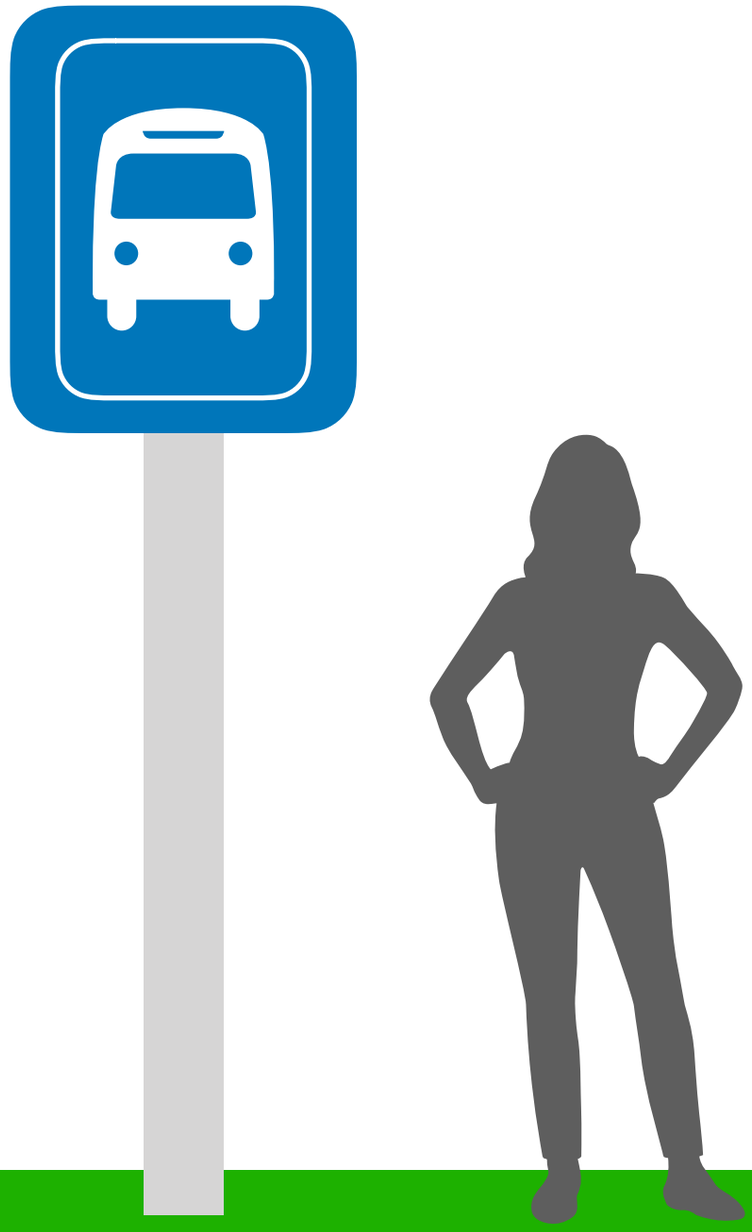


- We have a probability model (Poisson) for the number of bikes you see every day
- Your model only has one parameter (lambda) that governs the mean and shape of the distribution



- You use the observed average number of bikes to estimate the lambda parameter of the model

Example



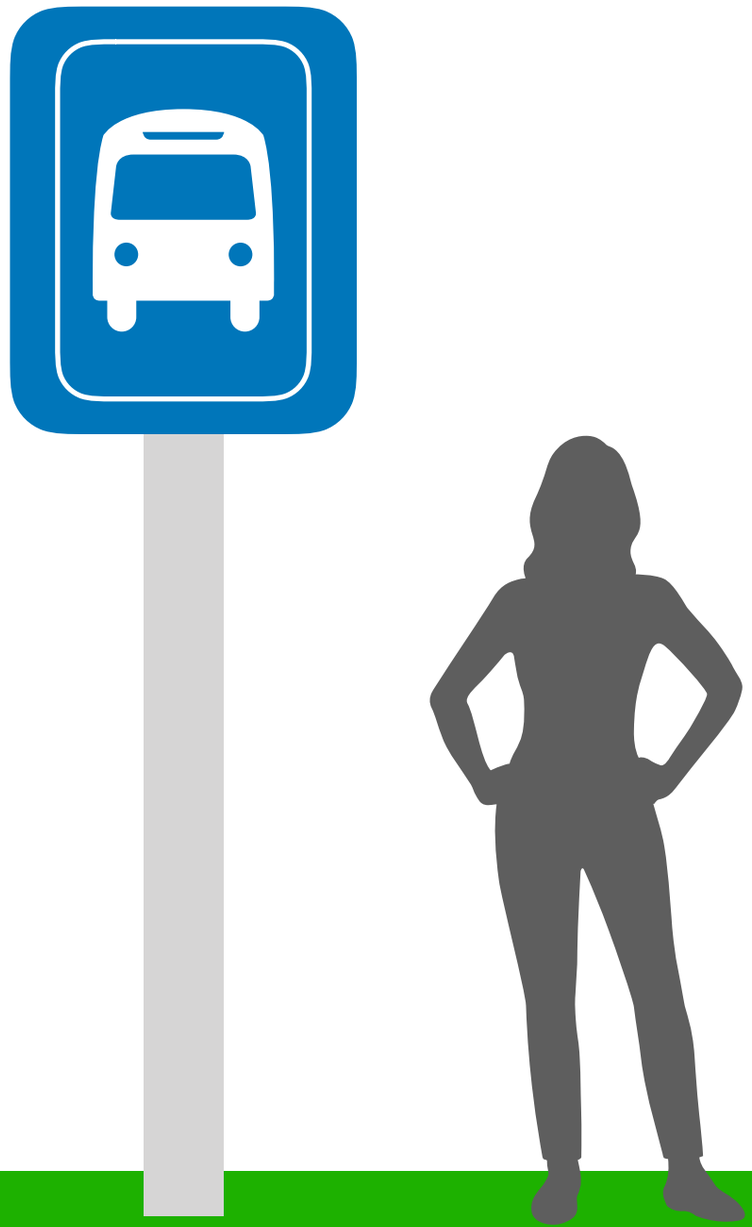
- We have a probability model (Poisson) for the number of bikes you see every day

Questions to ask:

- Does the model capture the mean behavior?
- Does the model capture the variability?
- Can we accurately get probabilities of extreme events: P(X=1000)?

-

Example



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Questions to ask:

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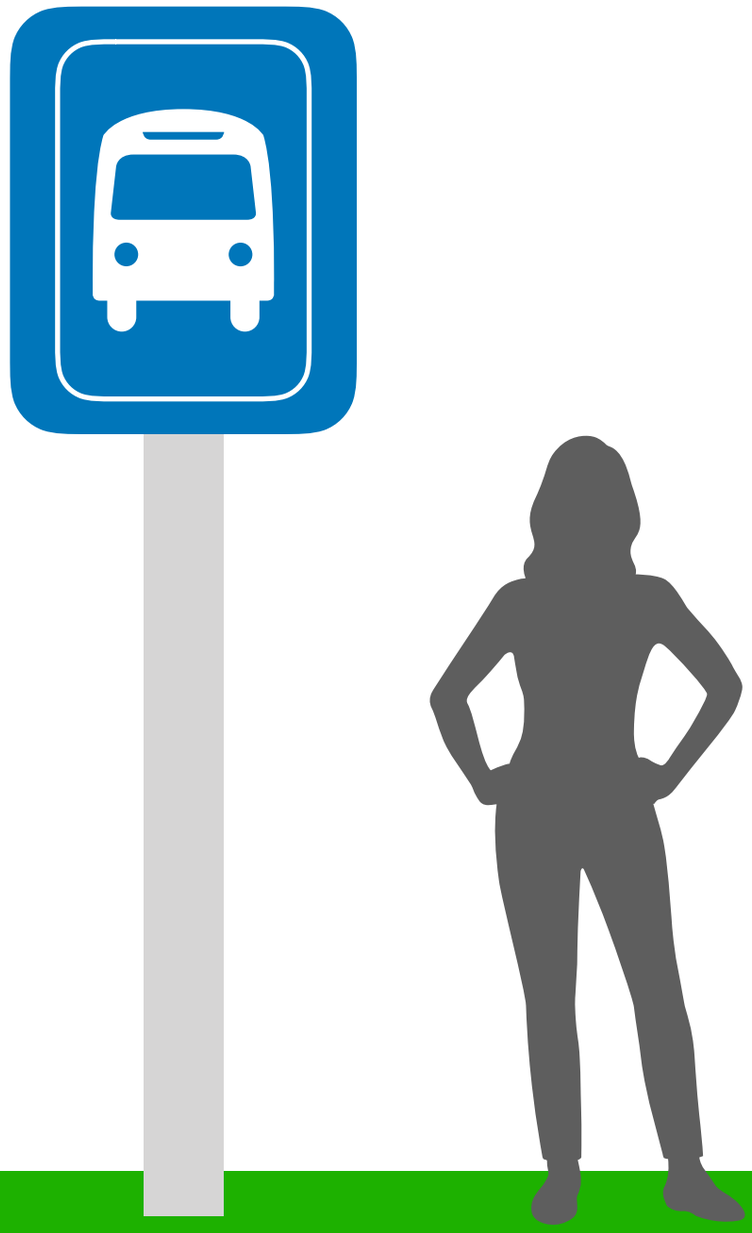
- Can we accurately get probabilities of extreme events: P(X=1000)?

Even if it is a good model, it will never be perfect:

- Only one parameter controls mean and shape of distribution
- We assume the same parameter for every day and for every hour of the day:
  - Day to day variability: not captured
  - Hour to hour variability: not captured
  - Weather: not captured

Example



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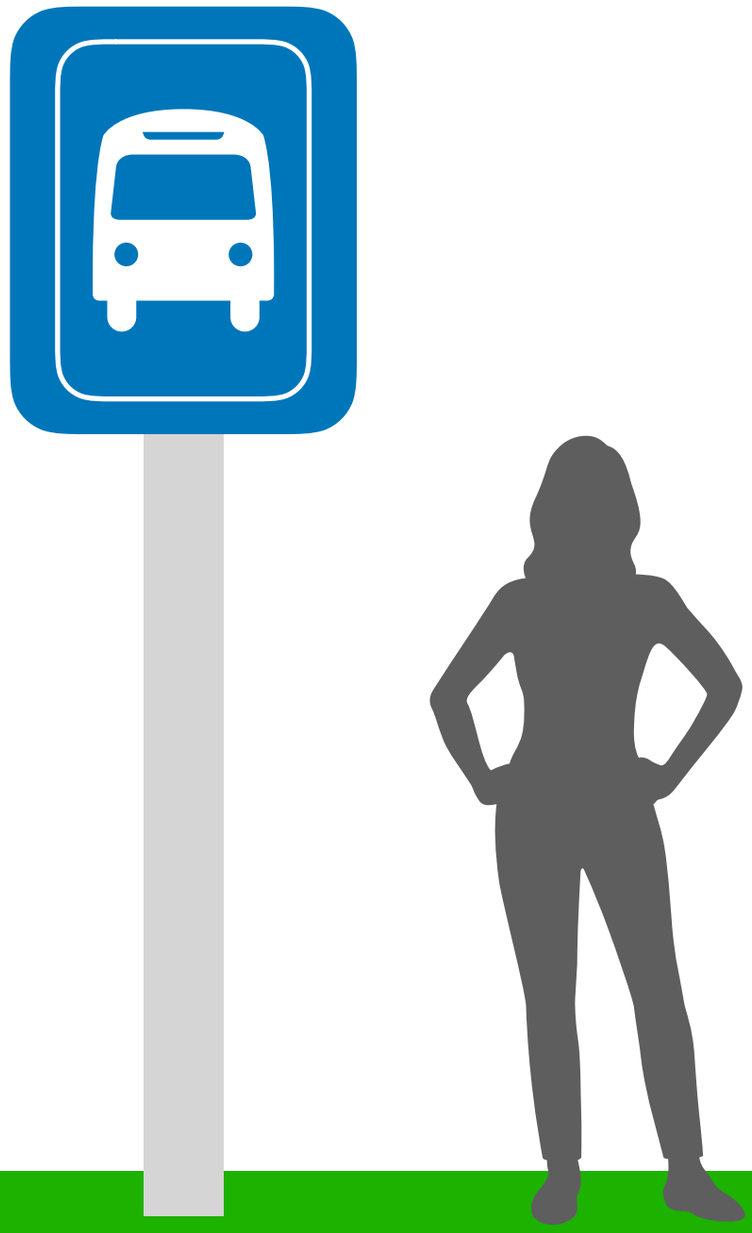

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It does not have to!

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All models are wrong,
but some models are
useful

George Box
Founder of UW Stat
department

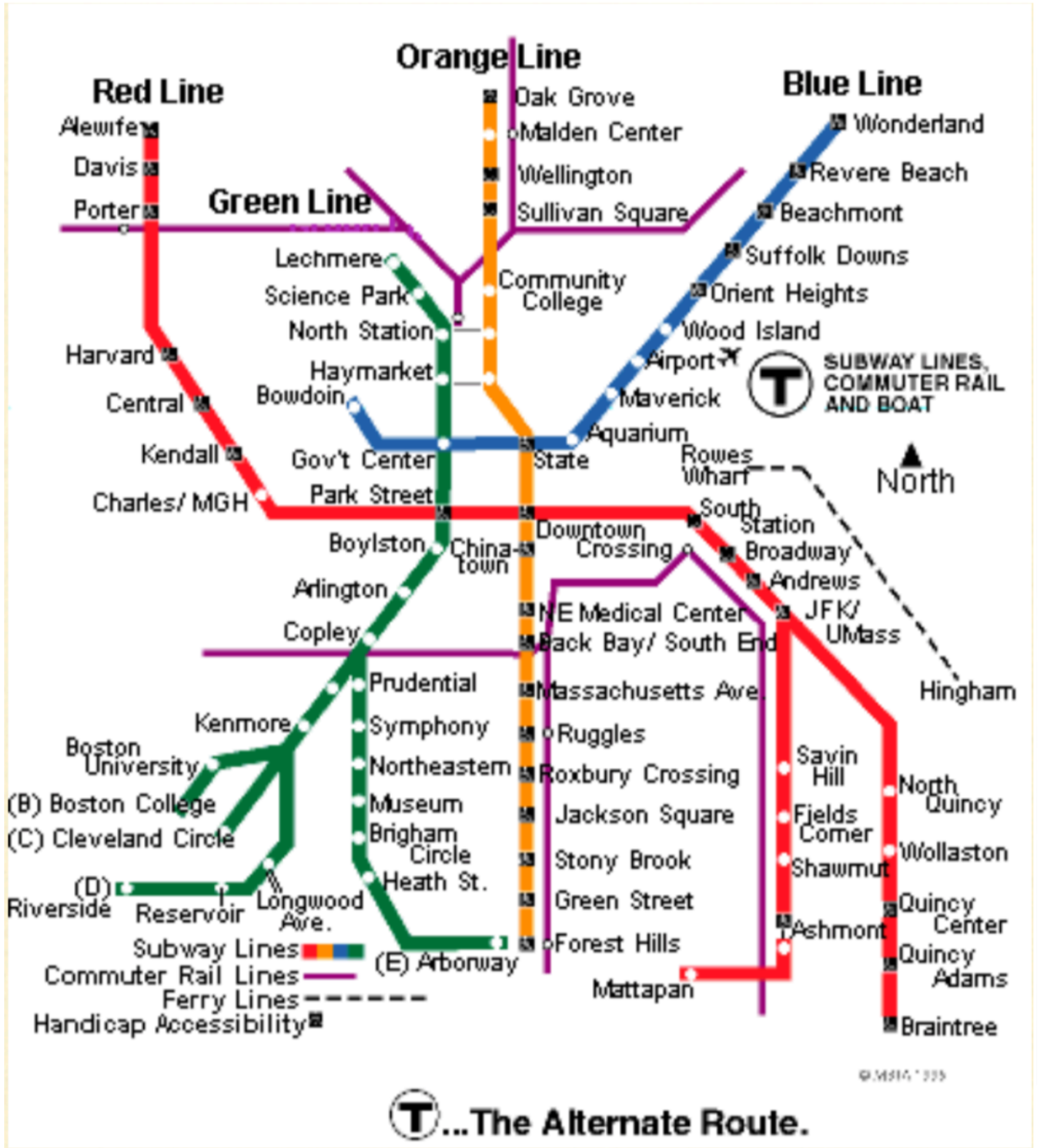
A very **realistic** subway map

Slide inspired by P. Lewis

A very **practical** subway map

Slide inspired by P. Lewis

Which one is more useful?



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How useful?

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How useful?

It will depend on the assumptions of the model and the quality of the input data

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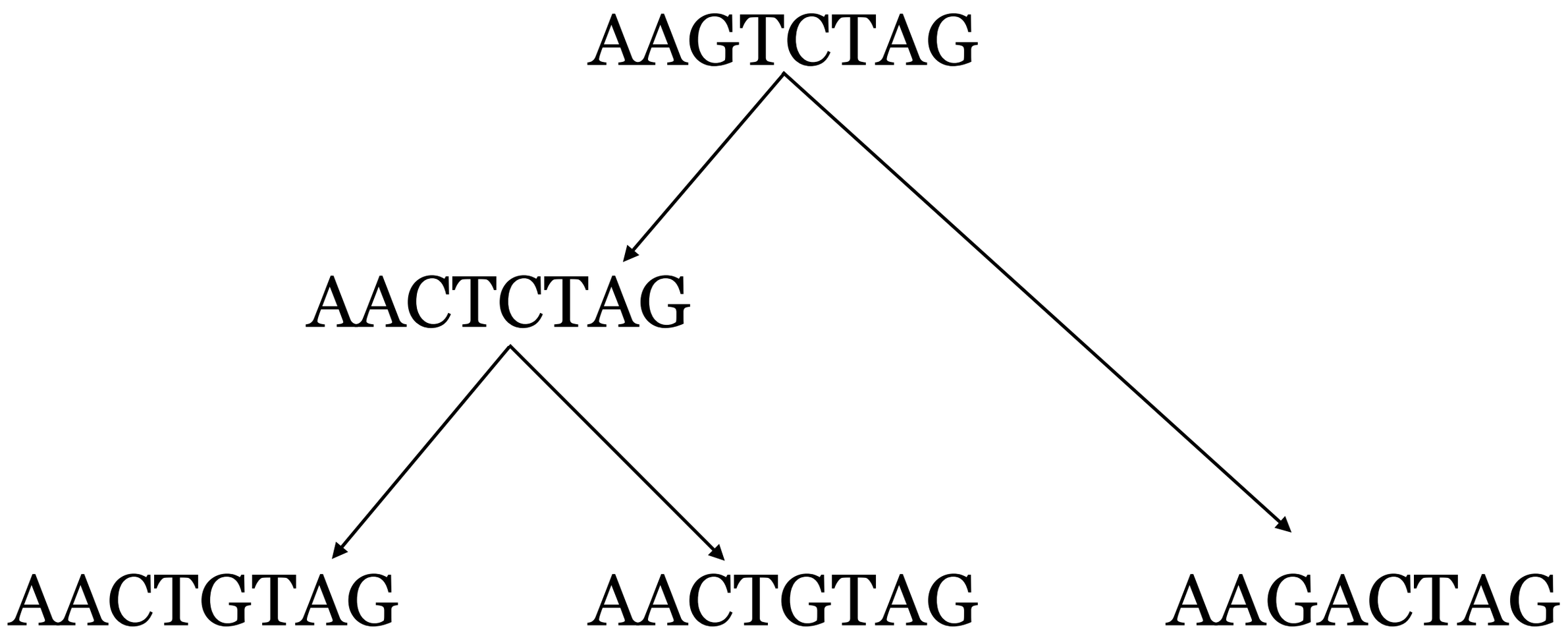
How useful?

It will depend on the assumptions of the model and the quality of the input data

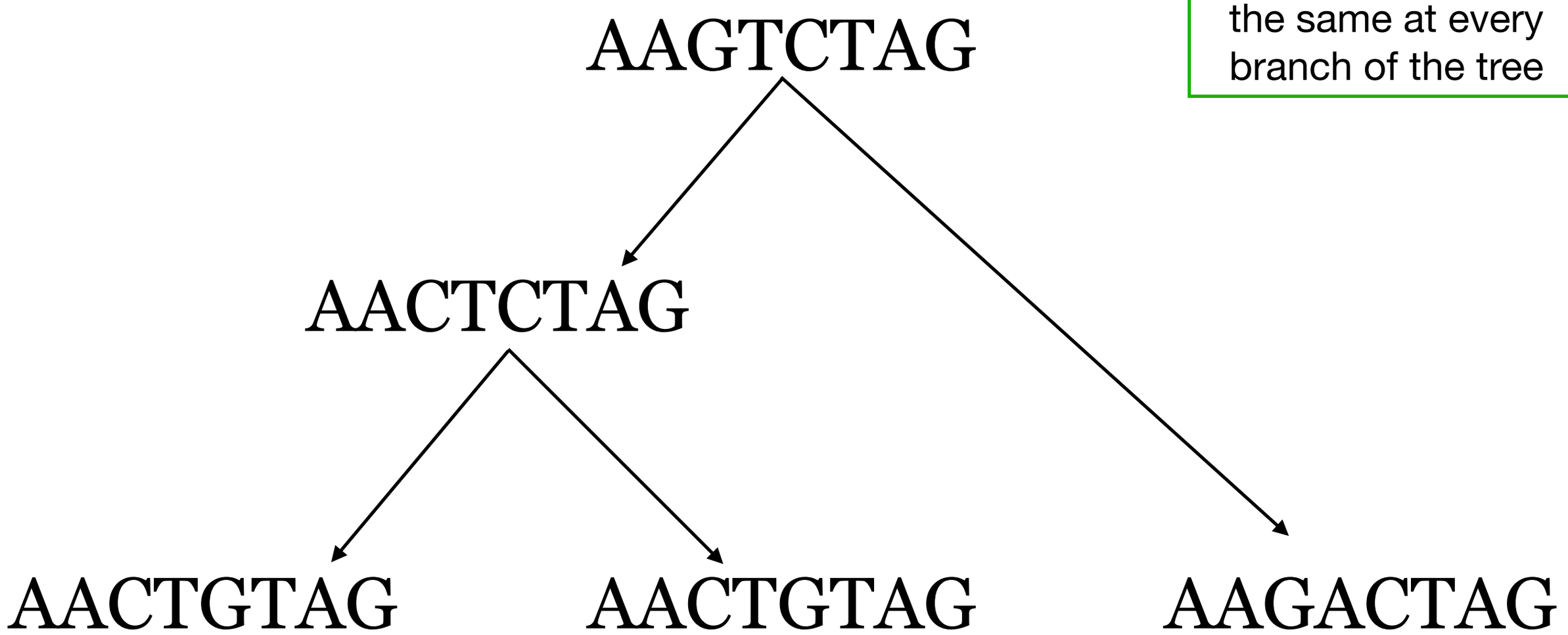
In our example, we count the number of bikes on n days

We need a probability model for the evolution of sequences along a phylogenetic tree



We need a probability model for the evolution of sequences along a phylogenetic tree

Assumption 1: The mutation process is the same at every branch of the tree



We need a probability model for the evolution of one ancestral sequence into a descendant sequence

AAGTCTAG

AACTCTAG

Assumption 1: The mutation process is the same at every branch of the tree

Implication: We only focus on the mutation process between two sequences

We need a probability model for the evolution of one ancestral sequence into a descendant sequence

Assumption 2: We assume sites evolve independently

AAGTCTAG

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We need a probability model for the evolution of an ancestral site into a descendant site

Assumption 2: We assume sites evolve independently

Implication: We can focus on the mutation process between two sites

We need a probability model for the evolution of an ancestral site into a descendant site

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Assumption 3: All sites evolve the same

We need a probability model for the evolution of an ancestral site into a descendant site

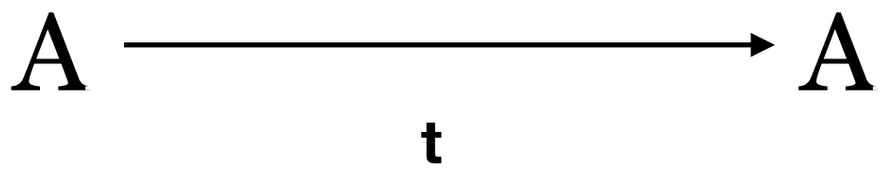
Assumption 2: We assume sites evolve independently

Implication: We can focus on the mutation process between two sites

Assumption 3: All sites evolve the same

Implication: We can choose any site to model the mutation process

We need a probability model for the evolution of an ancestral site into a descendant site



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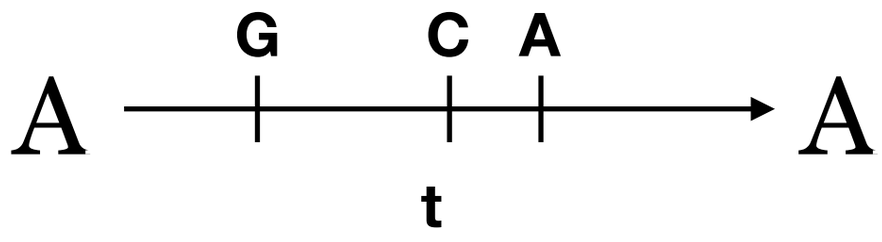

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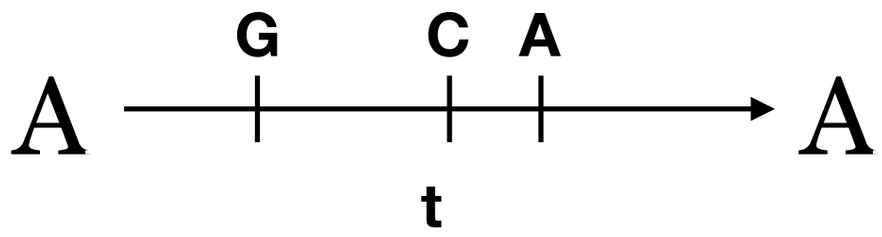
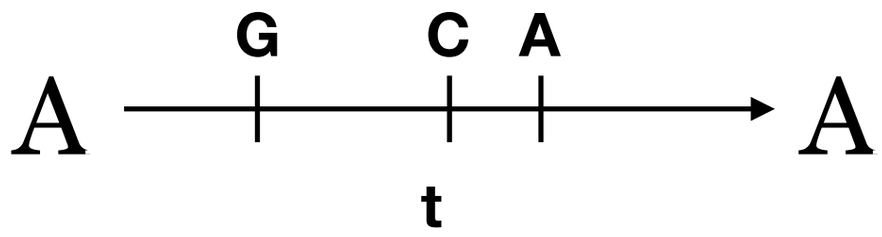


Number of mutations on time t is assumed to follow a Poisson distribution

$$P(X = k) = \frac{(\mu t)^k e^{-\mu t}}{k!}$$

We need a probability model for the evolution of an ancestral site into a descendant site



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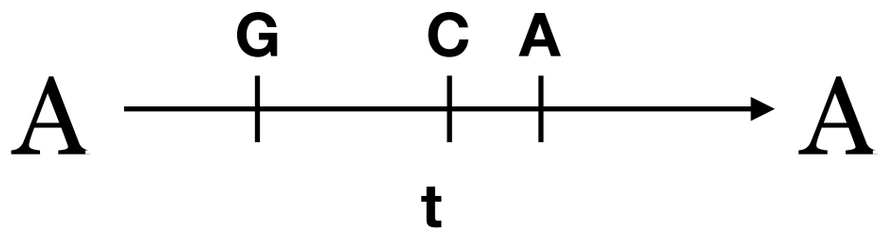
Rate of mutation events

We need a probability model for the evolution of an ancestral site into a descendant site



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Rate of mutation events

Expected number of mutation events in time t

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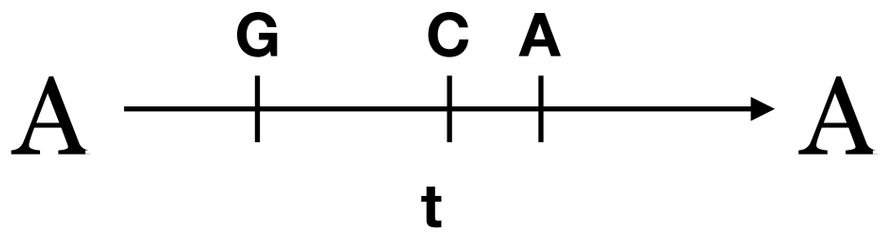

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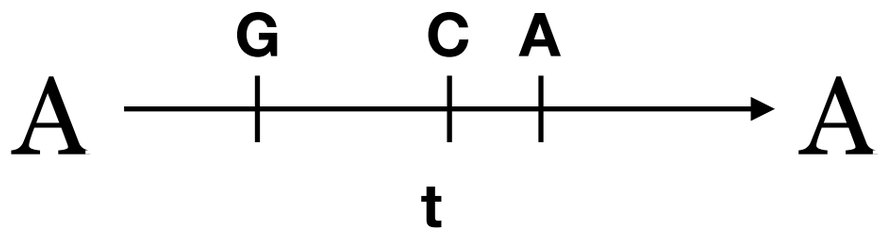
Rate of mutation events

Expected number of mutation events in time t

* Note that “mutation events” are not the same as substitutions because A->A is considered a mutation event

We need a probability model for the evolution of an ancestral site into a descendant site



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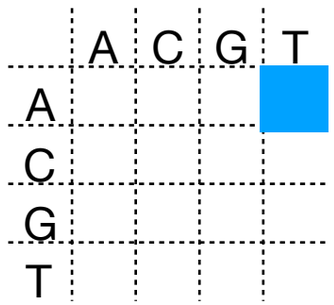
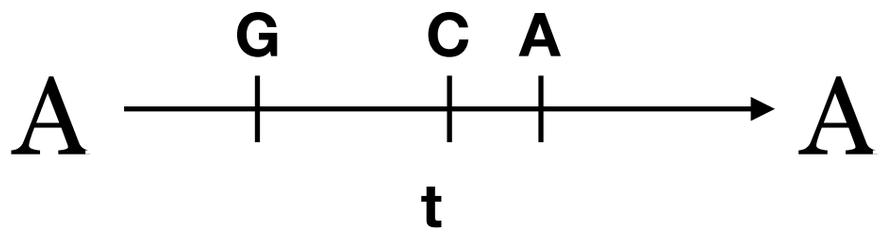
Probability matrix $\mathbf{R} =$



Probability of changing from state A to state T

We need a probability model for the evolution of an ancestral site into a descendant site



Number of mutations on time t is assumed to follow a Poisson distribution

$$P(X = k) = \frac{(\mu t)^k e^{-\mu t}}{k!}$$

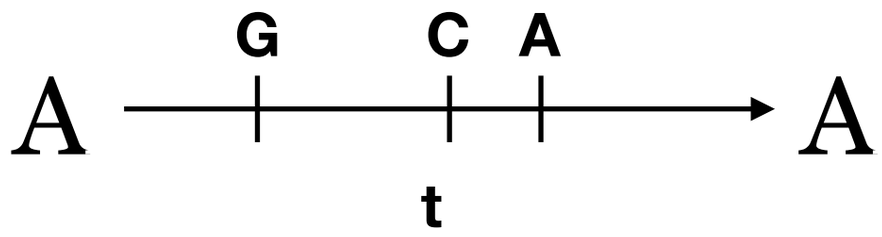
$$\mathbf{R} =$$

	A	C	G	T
A				
C				
G				
T				

Probability matrix $\mathbf{P}(t) =$

	A	C	G	T
A				
C				
G				
T				

We need a probability model for the evolution of an ancestral site into a descendant site



Number of mutations on time t is assumed to follow a Poisson distribution

$$P(X = k) = \frac{(\mu t)^k e^{-\mu t}}{k!}$$

$$\mathbf{R} =$$

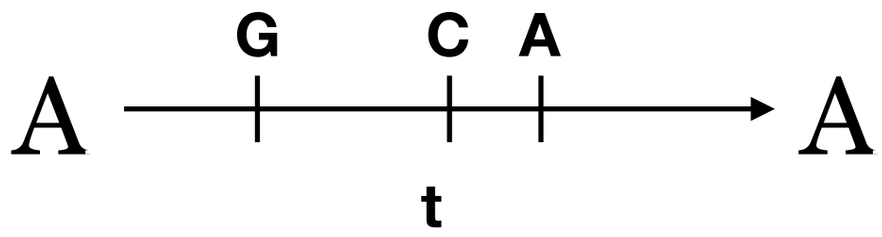
	A	C	G	T
A				
C				
G				
T				

Probability matrix $\mathbf{P}(t) =$

	A	C	G	T
A				
C				
G				
T				

← Probability of starting on A and ending on T in time t

We need a probability model for the evolution of an ancestral site into a descendant site



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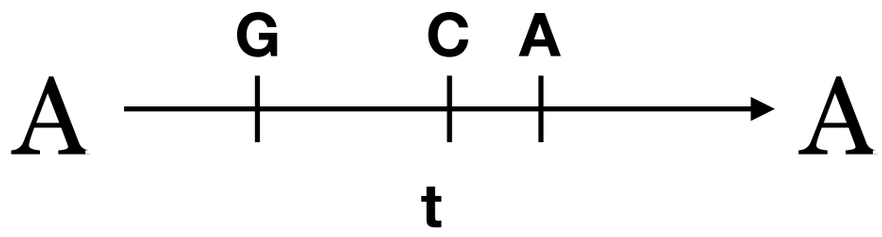
$$= \sum_{k=0}^{\infty} (\mathbf{R}^k) \frac{(\mu t)^k e^{-\mu t}}{k!}$$

Probabilities of change summed over all possible values of k (number of events)

We need a probability model for the evolution of an ancestral site into a descendant site



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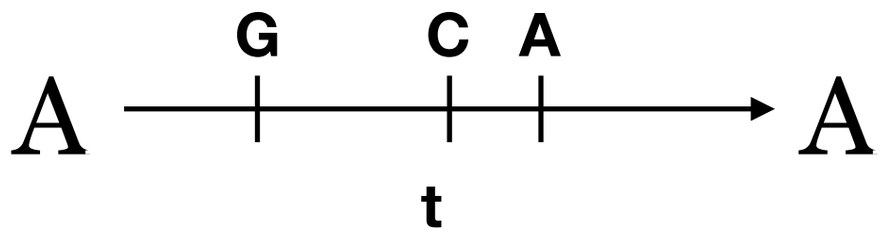

Number of mutations on time t is assumed to follow a Poisson distribution

$$P(X = k) = \frac{(\mu t)^k e^{-\mu t}}{k!}$$

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After some matrix algebra

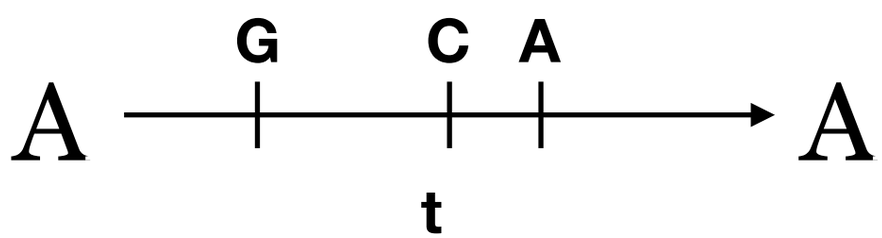
$$e^{\mathbf{Q}\mu t} = \mathbf{P}(t) = \begin{array}{c|cccc} & A & C & G & T \\ \hline A & & & & \\ C & & & & \\ G & & & & \\ T & & & & \end{array} = \sum_{k=0}^{\infty} (\mathbf{R}^k) \frac{(\mu t)^k e^{-\mu t}}{k!}$$

Instantaneous rate matrix (generator)

$$\mathbf{Q} = \mathbf{R} - \mathbf{I}$$

Probabilities of change summed over all possible values of k (number of events)

We need a probability model for the evolution of an ancestral site into a descendant site



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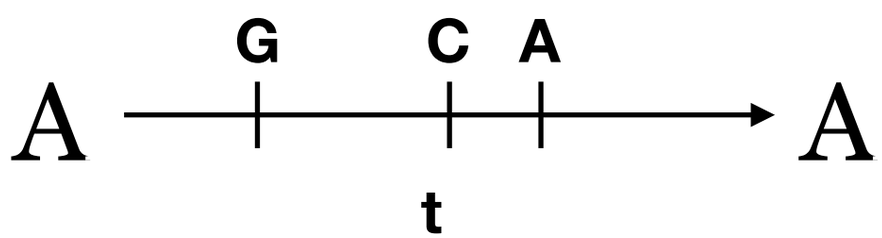
Substitution model

We need a probability model for the evolution of an ancestral site into a descendant site



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Substitution model

Choosing a substitution model means choosing Q:

$$\mathbf{Q} = \begin{pmatrix} -q_A & q_{AC} & q_{AG} & q_{AT} \\ q_{CA} & -q_C & q_{CG} & q_{CT} \\ q_{GA} & q_{GC} & -q_G & q_{GT} \\ q_{TA} & q_{TC} & q_{TG} & -q_T \end{pmatrix}$$

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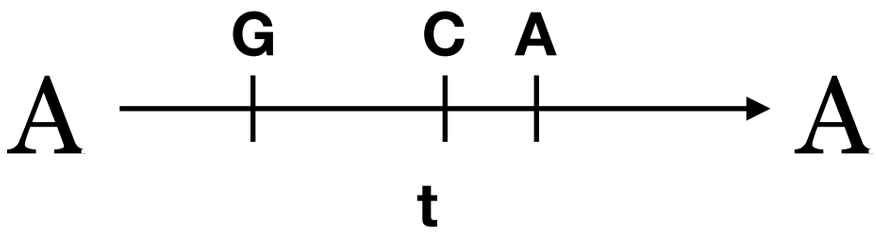

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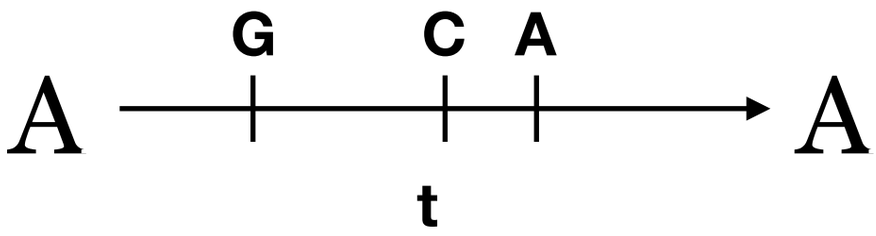
Substitution model

Homogeneous Continuous-time Markov chain on 4 states: A,C,G,T

We need a probability model for the evolution of an ancestral site into a descendant site



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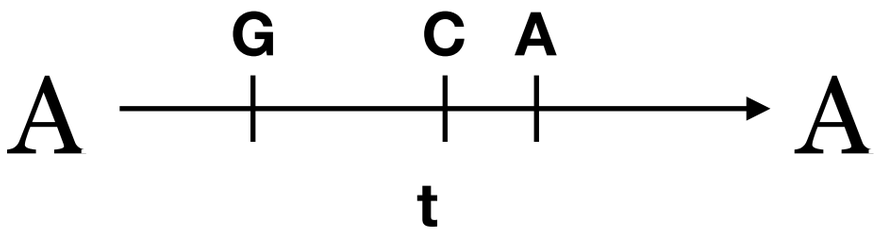
Substitution model

Homogeneous Continuous-time Markov chain

Probabilities for the next event do not depend on the time point where the chain is

We need a probability model for the evolution of an ancestral site into a descendant site



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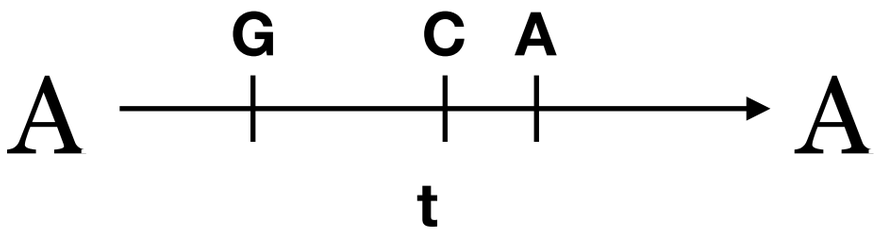
Substitution model

Homogeneous Continuous-time Markov chain

Probabilities for the next event do not depend on the time point where the chain is

Event can happen at any time point (not just discrete steps)

We need a probability model for the evolution of an ancestral site into a descendant site



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Substitution model

Homogeneous Continuous-time Markov chain

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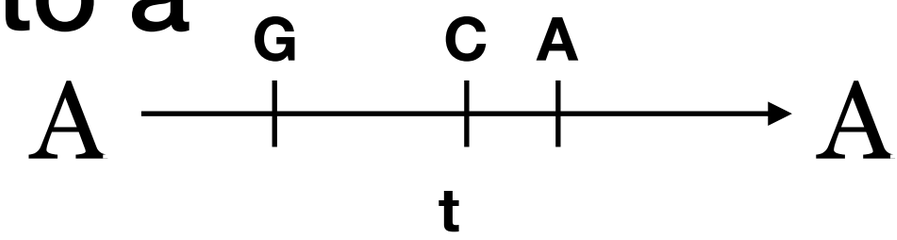
Probabilities of the next state only depend on the current state

We need a probability model for the evolution of an ancestral site into a descendant site



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Substitution model

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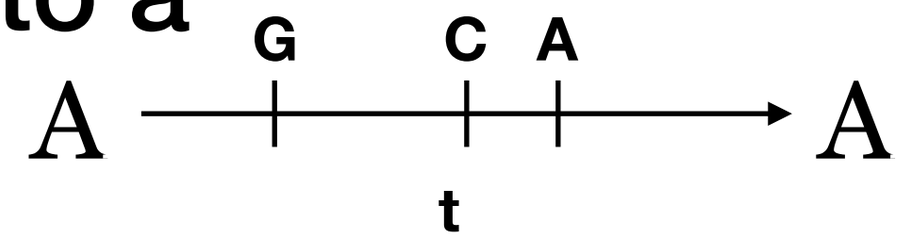

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Substitution model

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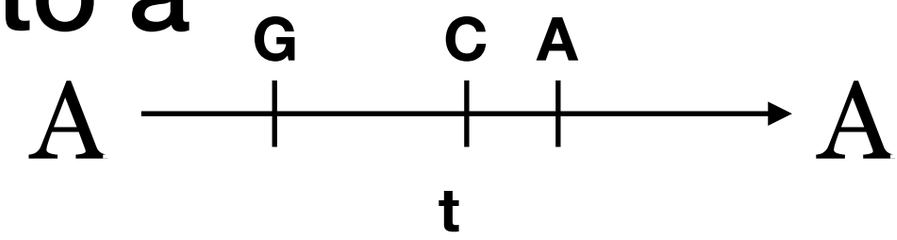
Event can happen at any time point (not just discrete steps)

Probabilities of the next state only depend on the current state

Other mathematical assumptions:

- **Ergodic:** As time goes to infinity, the probability that the site is in some state y is non-zero and independent of the starting state (there is a stationary distribution)
- **Time reversible:** The probability of sampling x from the stationary distribution and going to state y is the same as the probability of sampling y from the stationary distribution and going to state x

We need a probability model for the evolution of an ancestral site into a descendant site



Homogeneous Continuous-time Markov chain

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Substitution model

Probabilities for the next event do not depend on the time point where the chain is

Event can happen at any time point (not just discrete steps)

Probabilities of the next state only depend on the current state

Ergodic and time reversible

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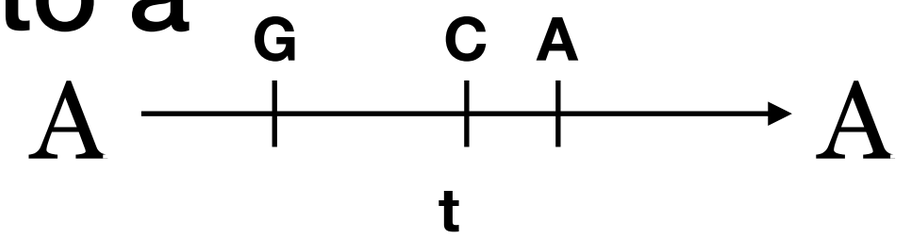

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Substitution model

Probabilities for the next event do not depend on the time point where the chain is

Event can happen at any time point (not just discrete steps)

Probabilities of the next state only depend on the current state

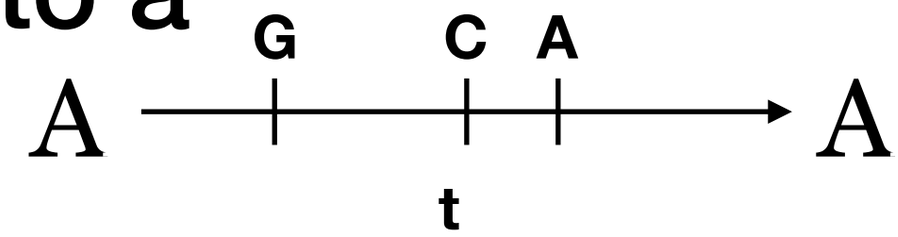
Ergodic and time reversible

Every substitution model that we will study has the same assumptions

Choosing a substitution model means choosing Q:

$$\mathbf{Q} = \begin{pmatrix} -q_A & q_{AC} & q_{AG} & q_{AT} \\ q_{CA} & -q_C & q_{CG} & q_{CT} \\ q_{GA} & q_{GC} & -q_G & q_{GT} \\ q_{TA} & q_{TC} & q_{TG} & -q_T \end{pmatrix}$$

We need a probability model for the evolution of an ancestral site into a descendant site



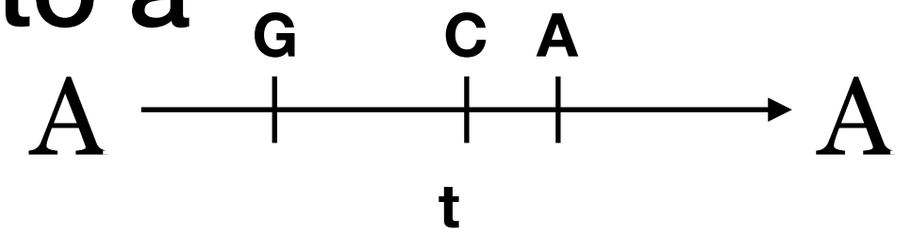
Jukes-Cantor model (JC69)

$$\mathbf{Q}_{JC69} = \begin{pmatrix} -3/4 & 1/4 & 1/4 & 1/4 \\ 1/4 & -3/4 & 1/4 & 1/4 \\ 1/4 & 1/4 & -3/4 & 1/4 \\ 1/4 & 1/4 & 1/4 & -3/4 \end{pmatrix}$$

$$\pi_A = \pi_C = \pi_G = \pi_T = 1/4$$

$$\mathbf{P}(t) = e^{\mathbf{Q}\mu t} \Rightarrow \begin{aligned} P_{ij}(t) &= \frac{1}{4} - \frac{1}{4}e^{-t\mu} \\ P_{ii}(t) &= \frac{1}{4} + \frac{3}{4}e^{-t\mu} \end{aligned}$$

We need a probability model for the evolution of an ancestral site into a descendant site



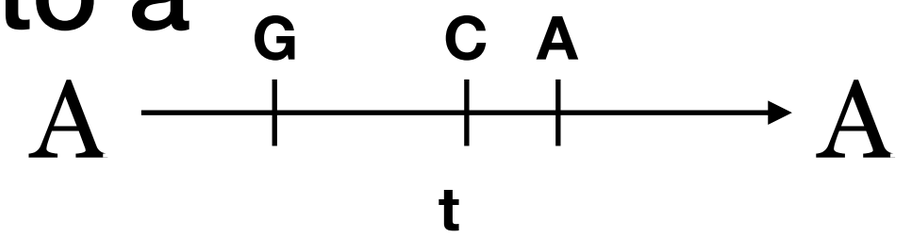
Felsenstein model (F81)

$$\mathbf{Q}_{F81} = \begin{pmatrix} -(\pi_C + \pi_G + \pi_T) & \pi_C & \pi_G & \pi_T \\ \pi_A & -(\pi_A + \pi_G + \pi_T) & \pi_G & \pi_T \\ \pi_A & \pi_C & -(\pi_A + \pi_C + \pi_T) & \pi_T \\ \pi_A & \pi_C & \pi_G & -(\pi_A + \pi_C + \pi_G) \end{pmatrix}$$

$$\pi_A, \pi_C, \pi_G, \pi_T$$

$$\mathbf{P}(t) = e^{\mathbf{Q}\mu t} \Rightarrow \begin{aligned} P_{ij}(t) &= \pi_j(1 - e^{-t\mu}) \\ P_{ii}(t) &= \pi_i + (1 - \pi_i)e^{-t\mu} \end{aligned}$$

We need a probability model for the evolution of an ancestral site into a descendant site



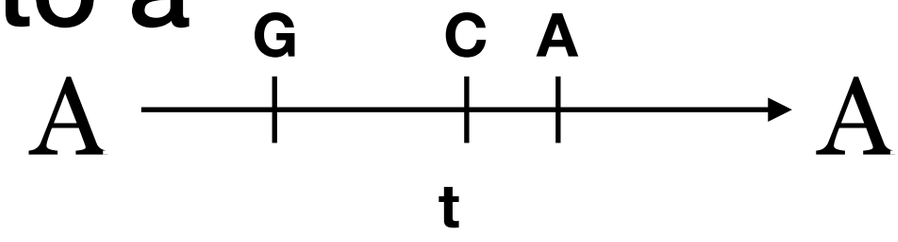
General Time Reversible (GTR)

$$\mathbf{Q}_{GTR} = \begin{pmatrix} -(a\pi_C + b\pi_G + c\pi_T) & a\pi_C & b\pi_G & c\pi_T \\ a\pi_A & -(a\pi_A + d\pi_G + e\pi_T) & d\pi_G & e\pi_T \\ b\pi_A & d\pi_C & -(b\pi_A + d\pi_C + f\pi_T) & f\pi_T \\ c\pi_A & e\pi_C & f\pi_G & -(c\pi_A + e\pi_C + f\pi_G) \end{pmatrix}$$

$$\pi_A, \pi_C, \pi_G, \pi_T$$

$$\mathbf{P}(t) = e^{\mathbf{Q}\mu t}$$

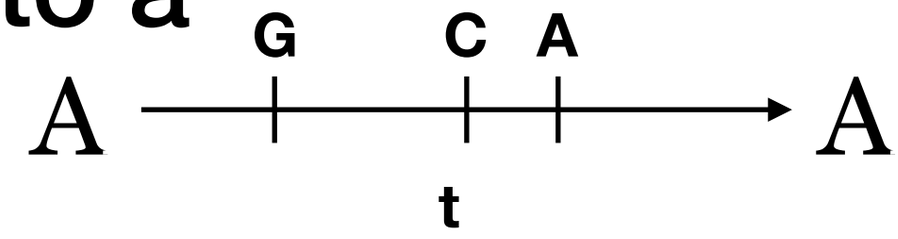
We need a probability model for the evolution of an ancestral site into a descendant site



Model	*Free parameters in the Q-matrix*
GTR	**8**
	$a, b, c, d, e, \pi_A, \pi_C, \pi_G,$ ($a+b+c+d+e+f=1$ $\pi_A+\pi_C+\pi_G+\pi_T=1$)
TN93	**5**
	$a=c=d=f$, $b=e, \pi_A, \pi_C, \pi_G,$ (*Ti/Tv ratio, Y/R ratio and and three frequencies since* $\pi_A+\pi_C+\pi_G+\pi_T=1$)
HKY85 **F84**	**4**
	$a=b=c=d=1$, $b=e=k, \pi_A, \pi_C, \pi_G,$ (*Ti/Tv ratio and only three frequencies since* $\pi_A+\pi_C+\pi_G+\pi_T=1$)
F81	**3**
	$a=c=d=f=b=e=f, \pi_A, \pi_C, \pi_G,$ (*only three nt frequencies since* $\pi_A+\pi_C+\pi_G+\pi_T=1$)
K80	**1**
	$a=b=c=d=1$, $b=e=k$, $\pi_A=\pi_C=\pi_G=\pi_T$ (*Ti/Tv ratio*)
JC69	**0**
	$a=b=c=d=e=f$, $\pi_A=\pi_C=\pi_G=\pi_T$

https://en.wikipedia.org/wiki/Models_of_DNA_evolution

We need a probability model for the evolution of an ancestral site into a descendant site



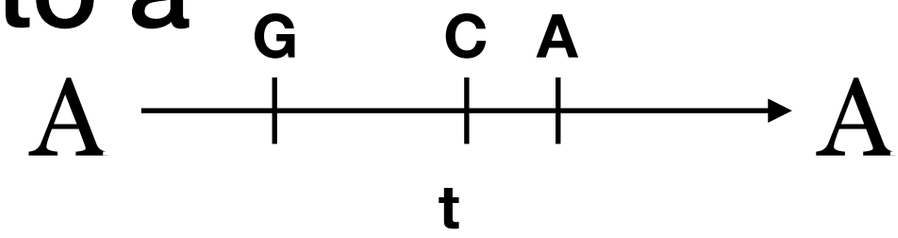
Jukes-Cantor model (JC69)

$$P_{ij}(t) = \frac{1}{4} - \frac{1}{4}e^{-t\mu}$$

$$P_{ii}(t) = \frac{1}{4} + \frac{3}{4}e^{-t\mu}$$

Rate of mutation: Scaling of branch lengths

We need a probability model for the evolution of an ancestral site into a descendant site



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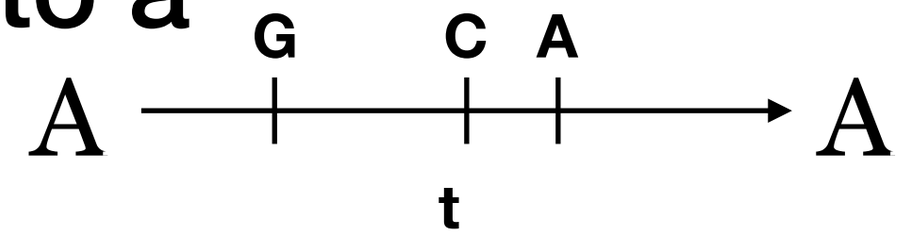
Expected number of mutation events in time t

Rate of mutation: Scaling of branch lengths

We need a probability model for the evolution of an ancestral site into a descendant site



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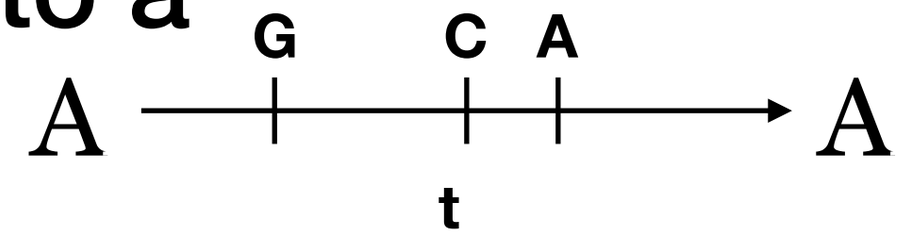
Expected number of mutation events in time t

Rate of mutation: Scaling of branch lengths

Problem: These mutation events include "redundant events" (A->A)

We need a probability model for the evolution of an ancestral site into a descendant site



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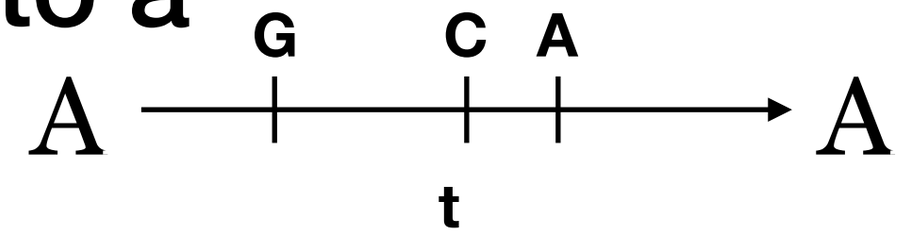
Expected number of mutation events in time t

Rate of mutation: Scaling of branch lengths

Problem: These mutation events include "redundant events" (A->A)

If we want branch lengths to reflect non-redundant substitutions per site, we need to **scale them appropriately**

We need a probability model for the evolution of an ancestral site into a descendant site



Jukes-Cantor model (JC69)

$$P_{ij}(t) = \frac{1}{4} - \frac{1}{4}e^{-t\mu}$$

$$P_{ii}(t) = \frac{1}{4} + \frac{3}{4}e^{-t\mu}$$

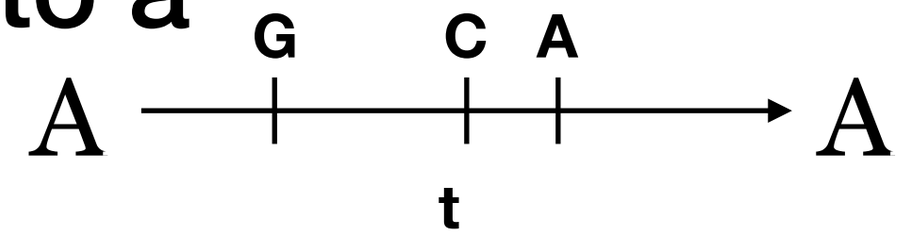
Rate of mutation: Scaling of branch lengths

Instead of having two parameters: $\mathbf{Q}, \mu$,
for a given $\mathbf{Q}$, we choose μ such that the overall rate of mutation is one. In this way, the length of the branch corresponds to the expected number of mutations per site along that branch (irrespective of the model)

More math-y: overall rate of mutation (expected number of non-redundant events in unit time t=1):

$$-\mu \cdot trace(\mathbf{\Pi Q})$$

We need a probability model for the evolution of an ancestral site into a descendant site



Jukes-Cantor model (JC69)

$$P_{ij}(t) = \frac{1}{4} - \frac{1}{4}e^{-t\mu}$$

$$P_{ii}(t) = \frac{1}{4} + \frac{3}{4}e^{-t\mu}$$

Rate of mutation: Scaling of branch lengths

Instead of having two parameters: $\mathbf{Q}, \mu$, for a given $\mathbf{Q}$, we choose μ such that the overall rate of mutation is one. In this way, the length of the branch corresponds to the expected number of mutations per site along that branch (irrespective of the model)

More math-y: overall rate of mutation (expected number of non-redundant events in unit time t=1):

$$-\mu \cdot trace(\mathbf{\Pi Q})$$

$$-\mu \cdot trace(\mathbf{\Pi Q}) = 1$$

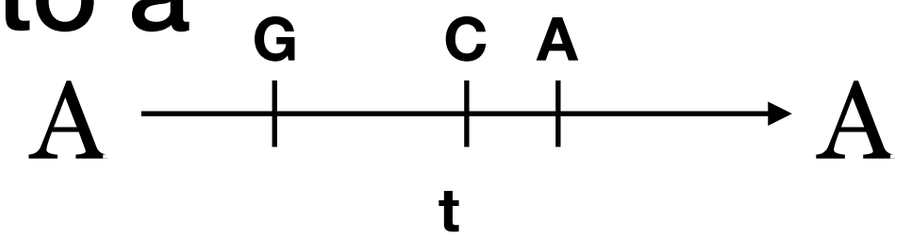
$$\mu = \frac{4}{3}$$

expected number of changes per site

$$P_{ij}(t) = 1/4 - 1/4e^{-4v/3}$$

$$P_{ii}(t) = 1/4 + 3/4e^{-4v/3}$$

We need a probability model for the evolution of an ancestral site into a descendant site



Homogeneous Continuous-time Markov chain

$$\mathbf{P}(t) = \begin{array}{c|cccc} & A & C & G & T \\ \hline A & & & & \\ C & & & & \\ G & & & & \\ T & & & & \end{array} = e^{\mathbf{Q}\mu t}$$

Substitution model

Probabilities for the next event do not depend on the time point where the chain is

Event can happen at any time point (not just discrete steps)

Probabilities of the next state only depend on the current state

Ergodic and time reversible

Branch lengths in expected number of substitutions, not time

We choose Q to select the substitution model we want

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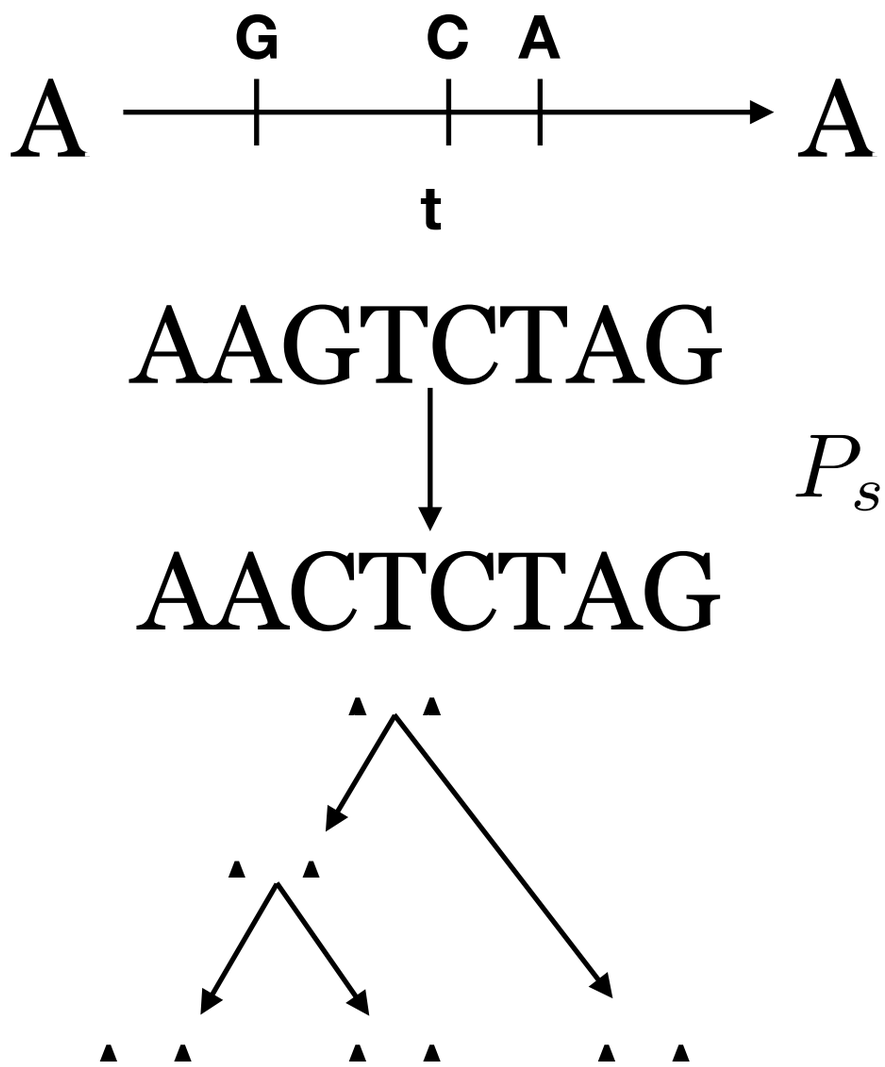
We need a probability model for the evolution of an ancestral site into a descendant site

We need a probability model for the evolution of one ancestral sequence into a descendant sequence

We need a probability model for the evolution of sequences along a phylogenetic tree



$P_{site}(t)$

Assumption 2: We assume sites evolve independently

Assumption 3: All sites evolve the same

$$P_{sequence}(t) = \Pi P_{site}(t)$$

Assumption 1: The mutation process is the same at every branch of the tree

$$P_{tree} = \Pi P_{branch}(t)$$

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Inferring pattern and process: maximum-likelihood implementation of a nonhomogeneous model of DNA sequence evolution for phylogenetic analysis. FREE

N Galtier, M Gouy

Molecular Biology and Evolution, Volume 15, Issue 7, July 1998, Pages 871–879,
https://doi.org/10.1093/oxfordjournals.molbev.a025991
Published: 01 July 1998

Biologically?

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jmb
Journal of Molecular Biology
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Regular article

Coevolving protein residues: maximum likelihood identification and relationship to structure [1]

David D. Pollock [1] [2] ✉, William R. Taylor [1], Nick Goldman [2]

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Same rate for every site

Among-site rate variation (ASRV)

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Published: September 1994

Maximum likelihood phylogenetic estimation from DNA sequences with variable rates over sites: Approximate methods

Ziheng Yang

Journal of Molecular Evolution **39**, 306–314(1994) | Cite this article

Among-site rate variation (ASRV)

- Variation of evolutionary rates across sites modeled by a continuous distribution
- The rate of a specific site *i* is not constant but a random variable *r(i)*
- The likelihood for site *i* is calculated by integrating over all possible rates
- The distribution of rates is usually assumed to be Gamma
- Instead of the numerical integration, a discrete distribution for rates tends to be used

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1861 Citations | **7** Altmetric | Metrics

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A slow site can become fast

Site-specific rate variation

covarion - heterotachy

Published: March 1971

Rate of change of concomitantly variable codons

W. M. Fitch

Journal of Molecular Evolution **1**, 84–96(1971) | Cite this article
93 Accesses | **84** Citations | Metrics

Comparative Study > Math Biosci. 1998 Jan 1;147(1):63-91.
doi: 10.1016/s0025-5564(97)00081-3.

Modeling the covarion hypothesis of nucleotide substitution

C Tuffley [1], M Steel

Affiliations + expand

PMID: 9401352 DOI: 10.1016/s0025-5564(97)00081-3 Paperpile

Summary

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We choose if we want ASRV

Branch lengths in expected number of substitutions, not time

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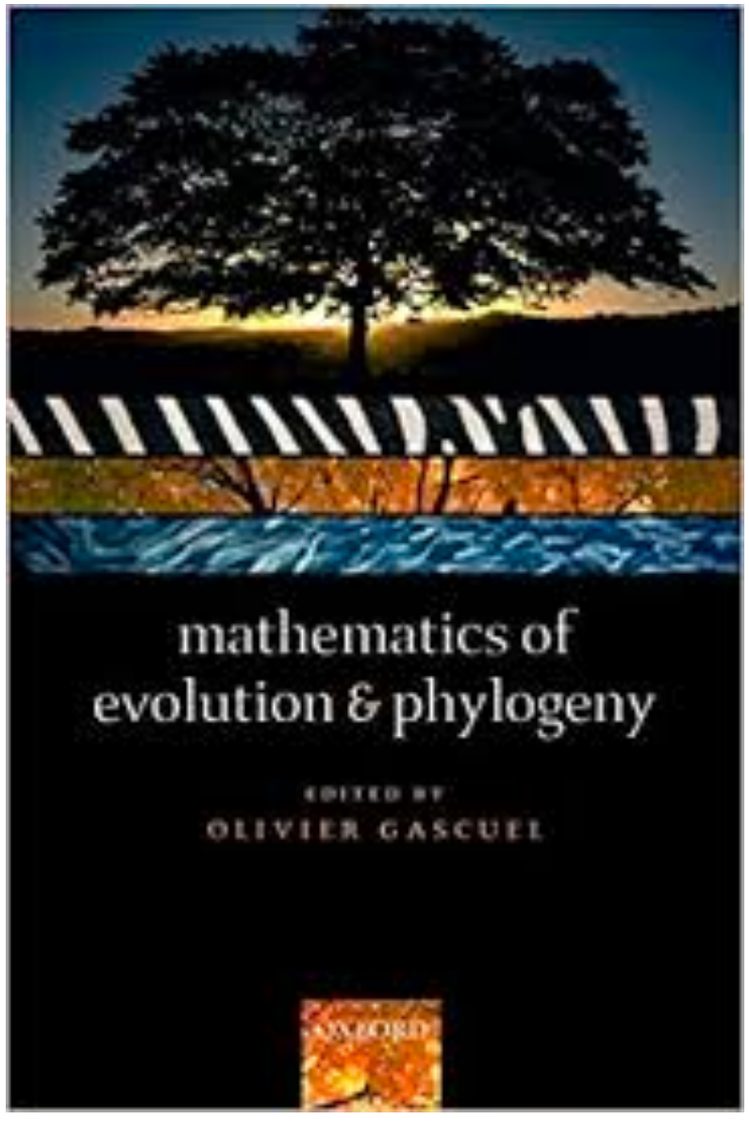
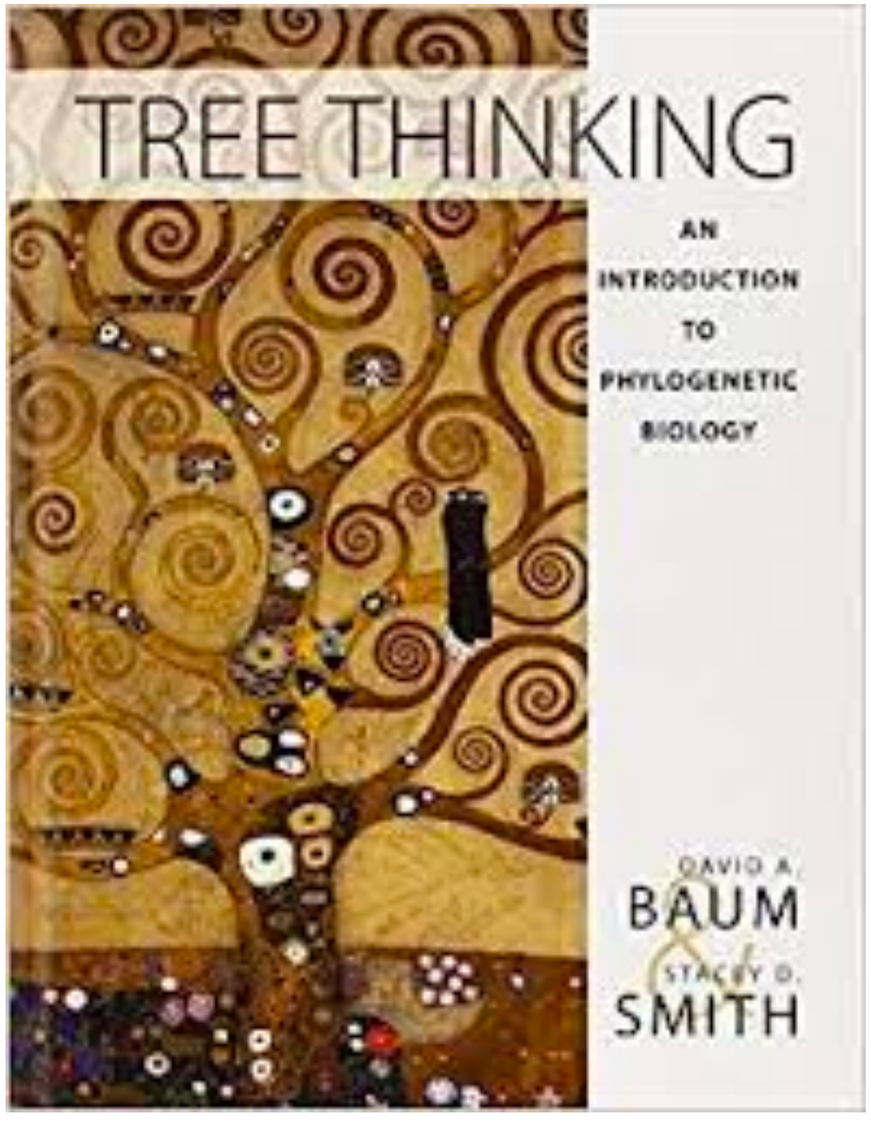
Further reading



Mathematics of evolution and phylogeny
Edited by Olivier Gascuel
Chapter 2



Tree thinking
David Baum and Stacey Smith
Chapter 8

How can anything work under such unrealistic assumptions?

“The purpose of models is not to fit the data, but to sharpen the questions”

–Samuel Karlin, 11th Fisher Memorial Lecture

Explicit model is thought as a limitation of likelihood, but it is a strength

All models are wrong,
but some models are
useful

George Box
Founder of UW Stat department

How useful?

It will depend on the assumptions of the model and the quality of the input data

In-class activity

- **Time:** 15 minutes

- **Instructions:** Let’s go over the different orthology methods that will be used in class